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SYNTHETIC POLY(1,3-DIOXOLAN-2-YLIC ACID)  
AND POLY(1,3-DIOXOLAN-2-YLIC ACID-B-CH<sub>2</sub>-CH<sub>2</sub>-CO<sub>2</sub>CH<sub>3</sub>)  
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**PROCEEDINGS OF THE AUSTRALIAN  
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Volume 32, Number 2

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**Supplement 1: International Thermal Physiology Symposium**

Wollongong, Australia

September 2<sup>nd</sup> – 6<sup>th</sup>, 2001

This special Issue of the *Proceedings of the Australian Physiological and Pharmacological Society* is dedicated to the papers presented at the **International Thermal Physiology Symposium** (Wollongong, Australia, September 2<sup>nd</sup> – 6<sup>th</sup>, 2001).

The **Thermal Physiology Symposium** is held every four years, and, since 1968, it has been timed to coincide with the **International Union of Physiological Sciences** Congress. The 2001 meeting was an official **IUPS** satellite meeting, sponsored by the Thermal Physiology Commission, and endorsed by both the Environmental Physiology and the Comparative Physiology Commissions. Delegates from 30 countries submitted more than 180 abstracts for this meeting, including 24 student presentations. Papers from this meeting appear in a special issue of the *Journal of Thermal Biology* Volume 26, 4-6.

This symposium is the last such specialised **IUPS** Thermal Physiology meeting. In future, symposia on the Pharmacology of Thermoregulation (last held in Seville, 1999: *Journal of Thermal Biology* 24: 287-482 and 25: 1-196) and the Physiology of Thermoregulation will be combined in a single meeting. The first such combined meeting will be held in Eilat, Israel. (September 6<sup>th</sup>-11<sup>th</sup>, 2004; contact Prof Michal Horowitz and Prof Yair Shapiro).

The principal sponsors for this symposium are:

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## **Submission of Abstracts**

There will be no Meeting of the Society in 2001, when the IUPS Meeting is to be held in Christchurch from August 26<sup>th</sup> to September 1<sup>st</sup>. (Congress Website <http://www.iups2001.org.nz>).

In 2002 the APPS Meeting will be part of the ASMR Health & Medical Research Congress, to be held in the Exhibition Centre in Melbourne in **November 25-29, 2002**

At present five societies will hold their major annual meeting and more than 13 other societies will hold symposia within the Congress.

Members should consult the APPS Website [www.apps.org.au](http://www.apps.org.au) for further information.

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**ABSTRACTS ARE ARRANGED IN ALPHABETICAL ORDER  
BY THE SURNAME OF THE FIRST AUTHOR**

## THE EFFECT OF SLEEP DEPRIVATION UNDER BRIGHT LIGHT CONDITION ON THERMOREGULATORY RESPONSES TO HYPERTERMIA

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It is well recognized that the circadian rhythm of resting internal temperature in humans shows a nadir in the early morning and a peak in the evening. Similarly, effector responses to thermoregulatory challenges show a circadian rhythm. For example, during heat stress (passive heat stress or dynamic exercise), internal temperature thresholds for thermoregulatory sweating and skin blood flow controls are subject to a circadian rhythm. Compared to dim light exposure, bright light exposure during sleep deprivation in the night leads to suppressed secretion of melatonin and attenuates the decline in internal temperature in the early morning. However, it is unknown whether thermoregulatory sweating and skin blood flow responses in the early morning are changed by the difference of internal temperature levels associated with light conditions during sleep deprivation. We investigated the effect of sleep deprivation under different light conditions on thermoregulatory responses to hyperthermia in the early morning. Six male subjects rested in a semi-supine position underwent nights of sleep deprivation in bright (2800 lux) light or dim (120 lux) light between 2100 hours and 0430 hours. Two experiments were performed in random order, and at least 1 week elapsed between experiments. After each sleep deprivation, passive heat stress was performed by immersing the legs below the knee in hot water (42 °C) for 50 minutes from 0530 hours. Sweating rate (SR) and skin blood flow (SkBF) were monitored on the chest and forearm. After hot water immersion, maximal cutaneous vascular conductance (CVC) was measured by locally warming the sites of SkBF measurement to 42 °C for 40 minutes. Urine levels of 6-sulfatoxymelatonin during sleep deprivation were lower under bright light exposure than that in dim light exposure. On the other hand, during sleep deprivation, rectal temperatures were maintained significantly higher in bright light condition compared with that in dim light condition. Similarly, before the hot water immersion, the esophageal temperature (Tes) measured during passive heat stress was significantly higher in bright light than in dim light condition. The time courses of SR and %CVC, expressed as a percentage of maximal CVC, were not statistically different between light conditions. The Tes thresholds for onset of sweating and cutaneous vasodilation were significantly higher in bright light than in dim light condition. However, each sensitivity of effector responses (the slope of %CVC or SR with respect to Tes) was not significantly altered between light conditions. These findings indicate that thermoregulatory sweating and skin blood flow responses to hyperthermia in the early morning are shifted by the attenuation of decreasing internal temperature levels during sleep deprivation with bright light exposure.

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## **ADENOSINE AND DOPAMINE AS NEUROMODULATORS IN HYPOXIC HYPOTHERMIA IN CONSCIOUS RATS**

*R.C.H. Barros and L.G.S. Branco, Department of Physiology, University of Sao Paulo, Ribeirao Preto, SP, Brazil.*

Adenosine has a depressant effect on neurons and its endogenous cerebral interstitial concentration increases with hypoxia. Dopamine also accumulates in the Nucleus Tractus Solitarius in response to peripheral chemoreceptor stimulation. No reports are available about the role of central adenosine and dopamine in the thermoregulatory and metabolic responses to hypoxia in conscious rats. Thus, we measured Tb by biotelemetry and oxygen consumption ( $Vo_2$ ) by closed respirometry of Wistar rats before and after intracerebroventricular injection of adenosine antagonist, aminophylline (40  $\mu$ g/1 $\mu$ l), or its vehicle (saline) and dopamine antagonist, haloperidol (0.5  $\mu$ g/1 $\mu$ l), or its vehicle (DMSO 5%) followed by a 30 min period of hypoxia exposure (7%  $O_2$ ). Both saline and DMSO 5% solution had no effect on Tb or  $Vo_2$  before and after hypoxic exposure. Neither aminophylline nor haloperidol changed Tb and  $Vo_2$  of rats during normoxia; however, during hypoxia both treatments significantly attenuated ( $P < 0.05$ ) hypoxic hypothermia and hypometabolism. In conclusion, this study indicates that central adenosine and dopamine seems to be neuromodulators involved in the hypoxic hypothermia. However, because aminophylline and haloperidol did not abolish the hypothermic response the study also suggests that action of several neuromodulators may be necessary to trigger a full-blown hypoxic hypothermia.

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## ROLE OF PREOPTIC AREA IN LPS-INDUCED BEHAVIORAL FEVER IN THE TOAD *BUFO PARACNEMIS*

*K. C. Bicego-Nahas and Luiz G. S. Branco, Faculty of Odontology of Ribeirao Preto and Faculty of Medicine of Ribeirao Preto -University of Sao Paulo, Ribeirao Preto, SP, Brazil.*

Preoptic-anterior hypothalamus (POA) plays an important role in thermoregulation in vertebrates. In mammals, it is known that fever can be initiated by a number of agents (including endotoxin - LPS). These are believed to release endogenous pyrogenic cytokines that may act on POA, which then stimulates the neural pathways inducing autonomic and behavioral responses that raise Tb. Amphibians, as all ectotherms, regulate their Tb primarily by behavior. Recently, we demonstrated that LPS causes behavioral fever in the toad *Bufo paracnemis* but the site in the central nervous system (CNS) involved in this response has not been assessed. Therefore, we tested the hypothesis that lesion of POA impairs behavioral fever induced by LPS in *Bufo paracnemis*. Toads were anesthetized in an aqueous solution of ethyl-*m*-aminobenzoate (submergence in 0.3% MS-222) and electrolytic lesions of POA were made. Measurements of preferred Tb were performed using a thermal gradient 4 days after surgery. After a control period of about 24 hours, control, sham-operated or lesioned toads were injected into the lymph sac with LPS (200 µg/kg) or pyrogen-free saline. Preferred Tb was monitored for 15 hours after injections. During control period, mean Tb was  $23.9 \pm 1.5$  °C and LPS caused a significant increase in Tb from the 8<sup>th</sup> to 11<sup>th</sup> hours after injection ( $P < 0.05$ ). There was no significant difference between control and sham-operated groups. Unilateral lesion of dorsal POA resulted in a delayed fever (from the 10<sup>th</sup> to 15<sup>th</sup> hours after LPS injection). Unilateral lesion of the ventral POA abolished behavioral fever induced by LPS. These results indicate that POA, especially the ventral portion, is an important area of the CNS of toads involved in behavioral fever.

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## TYMPANIC TEMPERATURE REACTION TO THE EXPOSURE TO ELECTROMAGNETIC FIELDS EMITTED BY CELLULAR PHONE

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Mobile phones have been in use since 1983, and the recent decade has seen their enormous proliferation. Their widespread use has caused that there has been a growing interest in the effect of electromagnetic fields (EMF) generated by the phones on the human organism. Mobile phones generate microwave radiation in the 450-1800 MHz frequency range. Although the exposure due to mobile phone use is below the admissible maximum values specified in the relevant standards, it is worth noting that the standards are based on expected thermal effects and do not take into account non-thermal effects. Accordingly, the admissible EMF radiation levels have been determined so as to prevent temperature growth of 2.2°C or higher in the exposed object. However, it would not be reasonable to assume that even less evident temperature growth (and within the brain in particular) is not able to cause harmful effects. Questionnaire surveys performed for example in Australia, Sweden and Norway on the subjective symptoms associated with the use of the mobile phones show that the most frequent symptoms include headache, vertigo, feeling of discomfort, sensation of warmth. The aim of the experiment was to assess the thermoregulatory response to EMF emitted by mobile phones. Studies of this subject are still sparse and incomplete. In our experiment seven young women, aged 19-29 (mean age 22.1±4.8) years were examined twice: on a day without exposure (control day) and on a day with continuous exposure (60 min exposure from cellular phone, frequency 800 MHz, output power 5 mW/cm<sup>3</sup>). All participants were qualified for the experiment upon their written consent. All the subjects were examined by a physician. The study was performed in the climatic chamber, the ambient temperature was about 26°C, relative humidity was 69%. The experiment started at 7 p.m. From 7 to 8 p.m. the subjects used cellular phone (on the one day the telephone emitted electromagnetic fields and on the second day it did not). The subjects were not informed which day was exposed and which control (without exposure). Starting from 8 p.m. till midnight the subjects listened to music and then they slept till 7 am. the next day. During the experiment the arterial blood pressure (BP), heart rate (HR) and the tympanic temperature (T<sub>ty</sub>) were monitored. Now we report data on the tympanic temperature. The tympanic temperature was measured every minute by thermistor probe (ST-21S, sensor Technica Co.) attached to the tympanic membrane from 7 p.m. to 12 p.m. hours. The data were analyzed using Wilcoxon matched-pairs signed-ranks test for each subject and for the whole group. We compared the tympanic temperature during the day with exposure (E) and during the control day (C) separately for 2 periods: (1) 7-8 p.m., (2) 8-12 p.m. Mean tympanic temperature during period 1 and period 2 differed significantly between E-day and C-day ( $p=0.0000$ ). Differences, however statistical significant, were very slight (about 0.01°C). The analysis of tympanic temperature of each subject revealed individual variations. Further investigations are being performed to explain these differences.

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## CAN FINGER DEXTERITY BE MAINTAINED WITH LOW FINGER BLOOD FLOW?

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The purpose of this project was to determine if high finger blood flow is required to maintain finger dexterity during cold exposure. Eight male subjects were exposed to two tests and one familiarization session over a time period spanning from July to September, 2000. During test one (designated as *EHV*), the hands were heated indirectly by using an electrically heated vest to actively heat the body, which in turn, resulted in an increased vasodilative response in the hands. The hands were insulated with thin, non-heated gloves and Arctic mitts. During test two (designated as *EHG*), the hands were heated directly using electrically heated gloves. Arctic mitts were worn over the EHGs. The finger skin temperature ( $T_{\text{fing}}$ ) during the *EHG* test was kept the same as the  $T_{\text{fing}}$  observed during the *EHV* test. During both tests, subjects sat in a lawn chair in a cold chamber maintained at  $-25^{\circ}\text{C}$  (wind  $\sim 2\text{km/h}$ ) for 3 hours. Arctic clothing insulation [ $0.556 \text{ m}\cdot\text{k}^2/\text{W}$  (3.6 Clo)] was worn over the body. During time 30-60 min and 135-165 min, subjects alternated between two finger dexterity tests [a C-7 rifle disassembly and assembly test (3-4 min duration) and 3 Purdue Pegboard (PP) tests (3-4 min duration)] during each 30 min test session. The Arctic mitts were removed during the dexterity tests.  $T_{\text{fing}}$  was measured using thermistors placed on the tips of the two "ring" fingers, and finger skin blood flow ( $Q_{\text{fing}}$ ) was measured using laser Doppler probes placed immediately next to the thermistors on the fingertip. Forearm muscle temperature ( $T_{\text{muscle}}$ ) was measured in the *m. flexor carpi radialis* muscle at a depth of 1.5 cm and a distance of approximately 9 cm distally from the medial epicondyle in the bulk of the muscle. Forearm surface temperature ( $T_{\text{surface}}$ ) was measured using a thermistor.  $T_{\text{fing}}$  was maintained at  $35.17 \pm 0.18^{\circ}\text{C}$  and  $34.37 \pm 0.25^{\circ}\text{C}$  during *EHV* and *EHG*, respectively, when the subjects were sitting still. During the dexterity tests  $T_{\text{fing}}$  was on average  $31.19 \pm 0.52^{\circ}\text{C}$  and  $29.53 \pm 0.86^{\circ}\text{C}$  during *EHV* and *EHG*, respectively.  $Q_{\text{fing}}$  was stable at  $224 \pm 27 \text{ PU}$  for 3 hrs during *EHV*, whereas during *EHG*,  $Q_{\text{fing}}$  decreased from  $133 \pm 26 \text{ PU}$  to  $39 \pm 8 \text{ PU}$  in 2 hrs and remained at that low level for the last hour.  $T_{\text{muscle}}$  was  $34.37 \pm 0.39^{\circ}\text{C}$  and  $32.62 \pm 0.39^{\circ}\text{C}$  during *EHV* and *EHG*, respectively.  $T_{\text{surface}}$  was  $32.06 \pm 0.45^{\circ}\text{C}$  and  $30.43 \pm 0.47^{\circ}\text{C}$  during *EHV* and *EHG*, respectively. C-7 rifle test performance was identical between conditions (i.e.,  $172 \pm 8$  sec). PP test performance was not significantly different between *EHV* and *EHG* (i.e., PP scores of  $22.2 \pm 1.2$  and  $20.5 \pm 1.9$  points, respectively). Finger dexterity was similar between conditions despite a significantly lower  $Q_{\text{fing}}$  during *EHG*. The similar performances suggest that  $T_{\text{fing}}$  is a more important factor than  $Q_{\text{fing}}$  in maintaining finger dexterity. Finger dexterity can be maintained even when finger blood flow is low.

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## MECHANISMS OF HYPOXIA-INDUCED HYPOTHERMIA

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Hypoxia evokes a regulated decrease in body core temperature (Tc) in a wide variety of organisms ranging from protozoans to mammals, a response that has been referred to as anapyrexia, but only recently did the mechanisms responsible for hypoxia-induced anapyrexia start to be suggested. A route mediating the reduction in Tc may be the impairment of central oxidative phosphorylation since intracerebroventricular injection of inhibitors of oxidative phosphorylation such as azide or cyanide reduces the preferred Tc of toads. Moreover, exclusion of glucose from central sites, which could impair oxidative phosphorylation, plays a major role in hypoglycemia-induced hypothermia. However, whether inhibition of oxidative phosphorylation acts directly on neurons to produce anapyrexia or is only a cellular signal for the release of substances that could mediate anapyrexia remains to be determined. Anyway, these data imply that the central nervous system (CNS) plays a central role in the development of anapyrexia. Several putative mediators of anapyrexia have been proposed. Some lines of evidence indicate arginine vasopressin (AVP) as a mediator. However, we recently showed that the blockade of AVP receptors peripherally as well as centrally does not alter the magnitude of hypoxia-induced anapyrexia. Data with Brattleboro rats, which lack AVP producing neurons in the CNS, also support this notion. Besides AVP, many other mediators have also been suggested such as lactate, adenosine and histamine, but none of the possible candidates can trigger a full blown hypothermic response. Recently, the labile gas nitric oxide (NO), by acting in the CNS, has been shown to play a major role mediating hypoxia-induced anapyrexia as well as the decrease in Tc elicited by other stimuli, such as 2-DG, insulin, and systemic arginine-vasopressin, suggesting that NO is a common mediator of hypothermia. This effect is likely to be dependent on the neuronal isoform of NO synthase since treatment with 7-NI, a selective neuronal NO synthase inhibitor, impairs hypoxia-induced anapyrexia, even though some controversy may exist. Furthermore, it is interesting to point out that recent data from our laboratory also points that substances may be formed during hypoxia to counteract the actions of the mediators of anapyrexia and, consequently, to avoid an excessive drop in Tc, similarly to what occurs during fever (pyrogens vs. cryogens). This seems to be the case of endogenously formed carbon monoxide (CO) since inhibition of the enzyme responsible for CO synthesis in the CNS augments the hypoxia-induced anapyrexia. Although progress has been made in the understanding of the mechanisms of anapyrexia, it is important to keep in mind that they still remain little explored and represent a field that needs urgent research.

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Support: FAPESP, CNPq, PRONEX.

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## NIGHT FEEDING OF GROWING CATTLE IN HOT SUMMER RELIEVES HEAT LOAD AND INCREASES GROWTH EFFICIENCY

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Under heat load conditions eating and digestion may cause an increased heat load if they coincide with the hotter part of the day. The studies were designed to assess the effect of time of feeding on the heat production (HP) pattern during the day and its effect on performance and efficiency. The data presented summarize studies over three summers, during about 90 days each year, in two feedlots: one unshaded, the other shaded by a 3 to 4 m high roof covering about one-third of the yard. Fattening calves, Holstein and beef breed, and growing beef heifers were used. In each feedlot each year animals were separated on the basis of breed, gender and age, and divided between two treatments: day and night fed. The day-fed animals received most of their feed during the day, and the night-fed animals received most of theirs during the night. Diet metabolizable energy (ME) was identical in the two treatments in each site and each year. Rectal temperature (Tr) and respiration rate (RR) were measured in the morning and in the afternoon. Body weight (BW) gain was measured monthly. Intake and efficiency were measured on a group basis, calculated monthly, and summarized for the entire trial. ANOVA statistical analysis was applied to the animal data and the pair comparison t-test was applied to the group data on animal gain, intake and efficiency (gain per intake). A treatment effect was accepted as significant for  $P < 0.05$ . During the 3 years we used 349 animals, separated into 11 groups in each treatment. Heart rate (HR) and skin temperature were measured throughout the day by data loggers attached to a harness strapped to the chest behind the forelegs. In one year, HP throughout the day was calculated by multiplying HR by the measured HP of one heartbeat, calculated from the oxygen consumption and HR simultaneous measurement. Rectal temperature was unaffected by the time of feeding in both feedlots. In the unshaded feedlot Tr was higher by  $0.3^{\circ}\text{C}$  in the afternoon than in the morning ( $P < 0.05$ ). Respiration rate (breaths/min) in the morning was not affected by the feeding regime; it was higher in the shaded feedlot than in the unshaded one, 61 and 52, respectively. In the shaded feedlot RR of the day and night fed animals increased in the afternoon by only 8 and 5 breaths/min, respectively; in the unshaded feedlot it increased by 49 and 34 breaths/min, respectively. The cattle manifested the lowest HP during the hotter hours of the day, when they were fed at night, but the whole-day HP was not significantly affected by feeding at night. In sum, the 3-year study on the group basis showed that dry matter (DM) intake was significantly reduced ( $P < 0.001$ ) by feeding at night: 7.628 and 6.961 kg/day for the day- and the night-fed animals, respectively. In spite of the lower intake of the night-fed cattle, their average growing rate was identical with that of the day-fed ones: 1.217 kg/day for both treatments. As a result, the gain per intake – the efficiency – was significantly increased by night feeding: 162.4 vs. 178.5 (g gain per kg DM intake,  $P < 0.005$ ) and 14.26 vs. 15.74 (g gain per MJ ME intake, ( $P < 0.005$ ) for the day-fed and the night-fed, respectively. The mechanisms that caused the significant increase of about 10% in the conversion of feed to growth are not clear, and further research is needed. Preliminary studies, in which we used a natural digestive tract the plant alkanes as low-absorbable markers, indicated a tendency for diet digestibility to be increased by about 5% by night feeding, compared with day-feeding.

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## OCCUPATIONAL ACCLIMATISATION TO HOT HEAVY WORK IN AUSTRALIAN BUSHFIRE FIGHTERS

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Generally, people who work in hot jobs are assumed to acclimatise to their work conditions. This report documents improvements in physiological heat tolerance acquired during fire fighting operations by a group of five male Australian bushfire fighters of age (mean and range) 25 (21-29) y and body mass 68.7 (63.1-79.1) kg. This 'natural acclimatisation' occurred over a period of 17 days in the summer. On seven of these days, at intervals varying from 3 consecutive days to 5 days apart, the firefighters worked to suppress large scale experimental forest fires. Fire suppression involved prolonged periods of strenuous work constructing fireline with hand tools. The work conditions in the seven fires were: work duration, 93 (42-190) min; air temperature, 30.6 (27.3-34.7)°C; mean radiant temperature, 71.9 (45.0-91.1)°C; water vapour pressure, 18.8 (16.7-22.2) mb; WBGT Index, 29.0 (24.3-34.4)°C; energy expenditure, 485 (439-616) w; estimated required evaporation (Ereq), 1,120 (1,018-1,347) g/h. The firefighter's work responses averaged for each individual for the seven fires were (mean and range): heart rate, 153 (143-162) b min<sup>-1</sup>; rectal temperature, 38.2 (37.9-38.6)°C; thigh skin temperature, 35.1 (33.5-35.9)°C; sweat rate, 1,175 (971-1,418) g/h. The evidence for acclimatisation is based on changes in the firefighters' responses between two occasions at about midday when they constructed fireline in the absence of fire; once before the 17 day period (Day 0, NF1), and again at the end of the period (Day 18, NF2). The work conditions and firefighters' responses in NF1 and NF2 are shown in the Table. Work heart rates, rectal temperatures, and thigh skin temperatures were all significantly lower, and sweat rates were also 10% lower in NF2 than in NF1. Increases (drifts) in heart rates and rectal temperatures with work time were less in NF2 than in NF1. Thigh skin temperatures increased with work time in NF1 but they decreased with work time in NF2. Rates of production of fireline were similar in NF1 and NF2.

Variables	NF1	NF2	NF2-NF1	P
<b>Work conditions (n=2)</b>				
Work duration min	151	141	-10	n.a.
Air temperature °C	33.1	32.0	-1.1	n.a.
Water vapour pressure mb	19.7	13.3	-6.4	n.a.
WBGT index °C	28.1	26.6	-1.5	n.a.
Energy expenditure w (n=5)	500	545	45	0.08
Required evaporation (Ereq) g h <sup>-1</sup> (n=5)	921	974	53	0.13
<b>Firefighters' work responses (n=5)</b>				
Heart rate b min <sup>-1</sup>	163	139	-24	0.008
Rectal temperature °C	38.48	38.12	-0.36	0.009
Thigh skin temperature °C	35.3	34.1	-1.2	0.001
Sweat rate g h <sup>-1</sup>	1,105	989	-116	0.033
Perceived exertion (RPE)	14.4	14.7	0.3	0.67

n.a. = not applicable

*Conclusion:* Seven exposures to fire suppression during a period of 17 days induced physiological adaptations characteristic of heat acclimatisation. Rather than increasing their work intensity with this acclimatisation these firefighters maintained their habitual work performance but enjoyed lower levels of physiological strain.

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## DRINKING BEHAVIOUR AND VOLUNTARY DEHYDRATION IN MEN SWEATING HEAVILY IN STRENUOUS OCCUPATIONAL WORK IN HOT WEATHER

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Dehydration results in impaired thermoregulatory and circulatory function, leading to loss of performance and increased risk of heat illness in prolonged heavy exercise or hot work. Yet, there do not appear to be effective physiological or behavioural mechanisms that ensure that drinking replaces sweat losses as they occur. This paper analyses 170 observations of water intakes and sweat losses made over 3 summer fire seasons on 30 male Australian bushfire fighters of age (mean and range) 26 (18-45) y and body mass 71.4 (51.7-105.0) kg. The observations arose from carefully conducted fluid balance studies that measured changes in body mass, food and water intake, and urine excretion, while the firefighters were engaged in fire suppression activities. On some days the firefighters worked on fires, on other days they performed the same work in the absence of fire. The firefighters were aware of the importance of preventing dehydration, and ample water supplies were readily available to them while they worked. For the 170 observations total work sweat losses were (mean and range) 2155 (615-4459) g, and sweat rates were 1127 (456-2373) g h<sup>-1</sup>. The rate of water intake (drinking) averaged 453 (0-1352) g h<sup>-1</sup>, which replaced 41 (0-96) % of sweat loss. Regression analysis revealed a significant but weak association between drinking rate and sweat rate ( $r = 0.55$ ,  $P < 0.0001$ ). An increase in sweat rate of 1,000 g h<sup>-1</sup> was associated with an increase in water intake of 350 g h<sup>-1</sup>, and conversely of 650 g h<sup>-1</sup> (about 0.9% body mass per hour) in the rate of dehydration. Because the percentage of sweat replaced varied so widely (0-96%), individual drinking behaviour was investigated in nineteen firefighters for whom there were from five to nine days of observation. Individual correlations between drinking rates and sweat rates ( $r$ ) averaged 0.63 (0.01-0.98). Two apparently distinct patterns of drinking behaviour were identified. In ten men (52%) the correlation between drinking rates and sweat rates ( $r$ ) was  $> 0.75$  ( $P < 0.10$ ) suggesting that their water intakes were consistently associated with their sweat losses. Based on their individual regressions, at a standardised sweat rate of 1200 g h<sup>-1</sup> these men's sweat replacements averaged 42 (24-57)%. In the other 9 men there were much weaker individual associations between water intake and sweat loss, although similar levels of sweat replacement of 43 (25-66)% were observed. The highest drinking rates observed in individuals averaged 812 (407-1305) g h<sup>-1</sup>, and the highest rates of individuals' sweat replacement averaged 62 (37-96) %.

**Conclusion:** Water intake and sweat loss appeared to be moderately to strongly associated in some men, while in others there was little or no association. Regardless of the pattern of individual drinking behaviour, water intakes failed to match sweat losses.

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## PHYSIOLOGICAL AND BEHAVIOURAL TEMPERATURE REGULATION IN MEN

### SUPPRESSING AUSTRALIAN SUMMER BUSHFIRES WITH HAND TOOLS

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Bushfire fighters undertake prolonged strenuous work, usually in hot summer weather, on fires that liberate great quantities of heat. How do they cope? Four seven-man crews were studied by reliable standard methods over three summers in Australian eucalypt forests while they attempted to suppress bushfires of intensities commonly faced by hand-tool crews (Budd *et al.*, 1997). They were men of age (mean and range) 26 (18-45) yr and body mass 71 (52-105) kg; they wore light cotton or wool coveralls, or trousers and shirt, together with boots and hard hat; and they experienced air temperature 29 (19-35)°C and mean radiant temperature 66 (33-96)°C, with low humidity and windspeed. *Physiological temperature regulation:* Firefighters' physiological responses averaged (mean  $\pm$  s.d.) energy expenditure (EE)  $516 \pm 100$  W, heart rate (HR)  $152 \pm 14$  beats  $\text{min}^{-1}$ , rectal temperature (Tre)  $38.2 \pm 0.2$ °C, thigh skin temperature  $34.5 \pm 1.7$ °C, and sweat rate  $1,144 \pm 373$  g  $\text{h}^{-1}$ . They considered the work 'somewhat hard' (Rating of Perceived Exertion (RPE)  $13.6 \pm 1.7$ ) and they felt 'just too warm'. No burns or heat disorders were observed. HR and Tre were not changed by a sixfold variation (36-217 min) in work duration, showing that their heat load was completely dissipated and they were in thermal equilibrium. Nor were HR or Tre changed by variations of 406-630 W in energy expenditure; of 15-34°C in Wet-bulb Globe Temperature (WBGT) — as much as 9°C above recommended limits; of 7-27% in body fat content; or of  $31-63 \text{ ml min}^{-1} \text{ kg}^{-1}$  body mass in maximum oxygen uptake, except for an attenuated effect on HR. These unchanged responses while firefighting are contrary to the results of numerous laboratory studies, and also to the firefighters' own responses in formal work tests. Effects of fire were negligible except for a  $356 \text{ g h}^{-1}$  increase in sweat rate, showing that the results are also applicable to other hot and/or strenuous occupations. *Behavioural temperature regulation:* The stability of HR and Tre during firefighting despite wide variations in work, weather, and fire, and in the firefighters' fitness, fatness, and age, is explained by (1) unrestricted evaporation of sweat and (2) firefighters' self-regulation of their work rate, radiant-heat exposure, and other work behaviour, guided by negative feedback from their physiological and subjective responses. Despite head-fire intensities as high as 3,280 kW per metre of fire front, firefighters' work practices reduced their radiant-heat exposure to an intensity ( $1.6 \text{ kW m}^{-2}$ ) little greater than that of sunlight, which could readily be blocked by clothing light enough to let sweat evaporate at rates of  $1-2 \text{ l h}^{-1}$ . The average metabolic heat load was more than twice the combined heat load from fire and weather, showing that the main task for bushfire fighters' clothing is not to keep heat out but to let it out. *Conclusions:* Behavioural regulation and appropriate clothing allowed firefighters to maintain their physiological and subjective responses at safe and sustainable levels over a wide range of job demands and personal factors. These findings highlight the limitations of laboratory studies for predicting physiological responses in the workplace.

Budd, G.M., Brotherhood, J.R., Hendrie, A.L., Cheney, N.P. & Dawson, M.P. (1997) Special Issue: Project Aquarius. Stress, strain, and productivity in wildland firefighters. *International Journal of Wildland Fire*, 7(2), 69-218.

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## ASSESSMENT OF THERMAL STRESS — THE ESSENTIALS

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The main reason for assessing thermal stress (hot or cold) in a workplace is to diagnose its causes and severity, and to provide guidance for the administrative and engineering changes that may be required to alleviate it. It is widely believed that this is a difficult, expensive, and time-consuming task. The aim of this paper is to show that, on the contrary, it can be done quickly and easily, by a single observer using simple and inexpensive instruments. The procedures described below are ones that my colleagues and I have found reliable in research projects and industry consultancies for more than 40 years. *Procedures:* We measure the thermal environment in the workplace (e.g. in a factory or a mine), and also in an adjacent shaded place outdoors to assess the prevailing weather. Three instruments suffice, namely (1) a sling (or Assmann) psychrometer; (2) an anemometer, preferably a non-directional thermo-anemometer; and (3) a globe thermometer — copper, matte black, and 15 cm in diameter. A fourth instrument, the natural wet-bulb thermometer, permits calculation of the Wet-bulb Globe Thermometer (WBGT) index of heat stress. (For a preliminary 'walk through' survey to detect sites requiring a more complete evaluation, the sling psychrometer is all that we need. Psychrometric measurements indoors and outdoors show to what extent air temperature (Ta) and water-vapour pressure (VP) in the workplace differ from those of the prevailing weather, while qualitative estimates of air velocity (AV) and radiant heat are provided by one of the most sensitive instruments available — the observer's face.) *Uses of the measurements:* From the above measurements, together with descriptions of the workers' clothing and activity, we can derive a great deal of useful information. First, we calculate VP and mean radiant temperature (MRT), thus completing our knowledge of the four primary quantities Ta, MRT, VP and AV. These provide an immediate impression of the level of thermal stress, and usually of its causes as well. Second, we calculate the extent to which MRT exceeds Ta in the workplace (i.e. the degree of added radiant heat — or vice versa in the cold), and the extent to which Ta, VP, and AV differ from those outdoors. All the above differences are due to the industrial process or other factors specific to the workplace, and they provide information about sources of thermal stress and the adequacy of ventilation. Moreover, by adding these differences to the outdoor values expected in different weather we can predict the likely workplace environment at such times. Third, we calculate, using the well known equations of Belding and Hatch, approximate but extremely useful estimates of the radiative, convective, metabolic, and total heat exchanges; of the extent to which the heat can be dissipated by the evaporation of sweat; and of the likely sweat rate and hence water requirements — estimates we have found to agree remarkably well with concurrent measurements of sweat rate. By repeating these estimates of heat exchange with different values of Ta, VP, etc. we can predict the likely effect in the workplace of different weather conditions, and of any engineering changes (e.g. radiation shielding or increased ventilation) that may be contemplated. Finally, we can calculate any desired index of thermal stress except those based on 'human analogue' devices such as the Botsball. *Conclusion:* By routinely measuring and evaluating the four primary quantities, and by estimating the workers' heat exchanges, we obtain a balanced and comprehensive assessment of thermal stress, and of the ways in which it might be alleviated.

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## HYPERTHERMIA-INDUCED NEURAL TUBE DEFECTS: THE PROTECTIVE EFFECT OF FOLIC ACID

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Maternal hyperthermia accounts for approximately 10% of all Neural Tube Defects (NTDs) and may be induced through febrile illnesses, spas and saunas, exertion in a hot or humid environment, as well as through a variety of pharmacological agents. NTDs arise when the neural tube fails to close and may result in a variety of disorders such as spina bifida and anencephaly. The neural tube is susceptible to teratogenic insult during the third and fourth weeks of gestation (postfertilisation), prior to the time when most women know they are pregnant. Administration of folic acid, a B-vitamin, can prevent up to 70% of all cases of NTDs. In this study whole embryo culture techniques are utilised to assess the potential protective effect of folic acid in hyperthermia-induced NTDs. Pregnant mice were killed on embryonic day 9 (E9) (plug day = E1) by cervical dislocation and embryos between 5 and 6 somites were pre-incubated with and without folic acid (0.1mL,  $2.9 \times 10^{-5}$  M) in a 38°C dry-air incubator for 30 min. Embryos were then exposed to a teratogenic hyperthermic episode (42°C) in a shaking water bath for 25min before being returned to a 38°C dry-air incubator for the completion of a 24h culture period. 5 somite embryos incubated without folic acid were the most susceptible to a hyperthermic episode of this dose, displaying generalised developmental retardation, while 6 somite embryos appeared morphologically normal. Interestingly, 5 to 6 somite embryos displayed highly localised developmental malformations confined to the craniofacial region while the remainder of the embryo remained unaffected. The highly localised malformation seen in these embryos suggest a susceptibility of neural crest cells, which migrate to form most of the craniofacial region. Addition of folic acid improved overall embryo size and improved morphogenesis in all embryos. Folic acid appears to have global protective effects in the presence of a teratogenic hyperthermic episode and these effects may extend to offer protection against exposure to other teratogens. Considering the susceptible period for a NTD is before neural tube closure in the fourth week of pregnancy it is important that folic acid is administered pre-conceptually.

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## NONSHIVERING THERMOGENESIS: THE UNIQUE ROLE OF BROWN ADIPOSE TISSUE

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It has become generally accepted that the heat deriving from brown adipose tissue metabolism provides a quantitatively significant contribution to the total heat required to defend body temperature when a rodent is placed in a cold environment. However, it has remained unclear as to whether this tissue alone is responsible for all adaptive nonshivering thermogenesis or whether other tissues can also be induced to contribute. This has become particularly pertinent with the discovery of genes, the sequences of which demonstrate high homology with the brown-fat specific uncoupling protein UCP1. The question is also relevant in larger animals not demonstrating discrete depots of brown adipose tissue. It has, however, now become possible to address these questions because of the availability of mice with a genetic ablation in the UCP1 gene. Brown adipose tissue thermogenesis is activated by norepinephrine released from sympathetic nerve terminals within the tissue. Injection of norepinephrine (1 mg/kg, i.p.) can mimic this reaction. Using the UCP1-ablated mice, we have been able to show that the response to injected norepinephrine consists of two components, a UCP1-dependent response, the magnitude of which is recruitable, and a UCP1-independent response which is not recruitable and which presumably corresponds to the metabolic response of all tissues to a high dose of a catecholamine. It is unclear whether the UCP1-independent response can ever be considered as physiological. Although the UCP1-ablated mice are, as expected, sensitive to cold, they can, nonetheless, be acclimated to survive in cold by a preacclimation period at an intermediate temperature. We have shown that their ability to survive at low temperature is entirely due to the ability of the animals to maintain persistent shivering. They have not developed any nonshivering thermogenesis in any tissue or organ, and survive presumably because of an improved endurance to shivering in the skeletal muscles. Thus, no other protein can compensate for the loss of UCP1 and no other hormone or neurotransmitter can replace norepinephrine in inducing any nonshivering thermogenesis. This demonstrates unequivocally that UCP1 homologues such as UCP2 or UCP3 are unable to be recruited and activated to be thermogenic under conditions of cold stress. Since it is becoming increasingly clear that loci of brown adipocytes are found in white fat depots, it is not improbable that even mammals lacking large visible brown adipose tissue depots nonetheless can recruit brown adipose tissue thermogenesis when required.

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## PARTICIPATION OF THE NITRIC OXIDE PATHWAY IN SEPSIS-INDUCED HYPOTHERMIA

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A few mechanisms have been suggested to be involved in sepsis-induced hypothermia, but no information exists on the role of nitric oxide (NO). In the present study, we assessed the participation of NO in sepsis-induced hypothermia by means of inhibition of NO synthase (NOS). Rats were anesthetized with 2,2,2-tribromoethanol and implanted with a polyethylene catheter into the jugular vein for administration of lipopolysaccharide (LPS) and a stainless steel guide cannula (0.7 mm o.d.) into the third cerebral ventricle for administration of the non-selective NOS inhibitor  $N^G$ -nitro-L-arginine methyl ester (L-NAME). After 1 week of recovery the body temperature of awake and unrestrained rats was measured over a period of 5 hours at 15 min intervals by inserting a thermoprobe into the colon. The body temperature was measured before and after administration of LPS (1.5 mg/kg), L-NAME (250  $\mu$ g/ 1  $\mu$ l) or both treatments together. In order to determine the effect of the NOS inhibitor on LPS-induced hypothermia, L-NAME was injected i.c.v. 30 min before LPS injection. Control animals received the same volume of D-NAME i.c.v and sterile saline i.v. Animals injected with LPS showed a significant decrease in body temperature 60 minutes after LPS administration from  $37.8 \pm 0.2$  to  $36.9 \pm 0.15^\circ$  C ( $P < 0.002$ ). In euthermic animals L-NAME caused no significant change in body temperature. However, when L-NAME and LPS were combined, a reduction in the magnitude of LPS-induced hypothermia was observed, from  $36.9 \pm 0.15$  to  $37.9 \pm 0.08$   $^\circ$ C ( $P < 0.001$ ). In conclusion, these findings are consistent with the notion that central NO pathway plays a key role mediating hypothermia elicited by endotoxaemia.

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## **THERMAL COMFORT AND BEHAVIOURAL STRATEGIES IN OFFICE BUILDINGS LOCATED IN A HOT-ARID CLIMATE**

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This paper discusses the main results of a large field study (Cena & de Dear, 1999) conducted in Kalgoorlie-Boulder, located in a hot-arid region of Western Australia, and focuses on the effects of indoor climates on thermal perceptions and adaptive behaviour of office workers. The study protocol followed the procedures for a series of large-scale ASHRAE (American Society of Heating, Refrigerating and Air-Conditioning Engineers) sponsored thermal comfort field surveys and included precise measurements of indoor climates with laboratory-grade instrumentation. Twenty two of the largest office buildings in Kalgoorlie-Boulder were chosen for the study. Sample sizes of 640 and 589 subjects were achieved in winter and summer surveys, respectively. This total of 1,229 sets of data was provided by 935 respondents, of whom 294 were interviewed in both seasons. Female subjects represented 48% of the sample. The average age of all subjects was 35 years. Clothing insulation levels were 0.5 clo in summer and 0.7 in winter. Office chairs were estimated to add 0.15 clo to the clothing insulation. Metabolic rates were estimated to be on average  $77 \text{ W/m}^2$  or 1.3 met for both seasons and for both sexes. Thermal neutrality, according to responses on the ASHRAE seven-point sensation scale, occurred at  $20.3^\circ\text{C}$  in winter and at  $23.3^\circ\text{C}$  in summer. Preferred temperature, defined as a minimum of subjects requesting temperature change, was  $22.2^\circ\text{C}$  for both seasons. Thermal acceptability showed little or no systematic relationship with the thermal environmental conditions. After the effect of chair insulation was accounted for, the PMV (Predicted Mean Vote) index adequately predicted optimum summer-time temperatures for the subjects, whether defined in terms of thermal neutrality, thermal acceptability or thermal preference. PMV overestimated neutrality by one and three degrees (C) in summer and winter respectively. On the basis of the adaptive model of thermal comfort one might have predicted that acclimatization to Kalgoorlie's hot and dry climate, especially during the summer season, would push the actual neutrality *warmer* than that predicted on the basis of PMV. One possible explanation for this counterintuitive outcome is that the occupants of air-conditioned buildings actually *adapt* to those indoor climates. There was little difference (particularly in summer) between the sexes in terms of thermal sensations, although there were significantly more expressions of thermal dissatisfaction from the females. The effects of Kalgoorlie-Boulder hot-dry/cool-dry seasonality on thermal comfort responses of office workers was significant, amounting to a  $3^\circ\text{C}$  shift in neutrality and was within the range expected on the basis of the clothing insulation differences of approximately 0.2 clo between seasons. Future research into how the overcooling of office buildings in hot-dry climates can be reduced without disrupting the comfort and productivity of their occupants is called for.

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## DEVELOPMENT OF A NOVEL THERMAL CONTROL SUIT FOR HUMAN THERMOREGULATION AND ENVIRONMENTAL ERGONOMIC STUDIES

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Cooling suits are becoming increasingly common in occupational and athletic settings in order to keep humans cool while working or exercising in hot environments. These cooling garments typically consist of vests containing packets of ice, or else liquid-cooling garments (LCGs) where conductive heat transfer is achieved by the movement of externally cooled water through narrow tubing stitched into the clothing. In research settings, LCGs can be used to heat or cool subjects by controlling the temperature of the water entering the LCG. We are in the development stage for a Thermal Control Suit (TCS) for use in thermophysiology and environmental ergonomic studies. The TCS is designed to extend the flexibility and limit of thermal control possible with present LCGs based on running water and an external heating/cooling source. The primary specifications for the TCS are the ability to, during either rest or light exercise: 1) maintain core temperature ( $T_c$ ) at a stable ( $\pm 0.10^\circ\text{C}$ ) level ( $T_c$  range  $35.0\text{--}40.0^\circ\text{C}$ ) for 60 min, 2) control the rate of  $T_c$  increase or decrease at a level of  $0.05^\circ\text{C}/\text{min}$ , 3) have multiple thermoregulatory controls for different body regions that can be independently controlled or combined in flexible configurations, and 4) accommodate individuals from 1.65-1.95 m. The TCS employs multiple (~30) thermo-electric modules (TEMs) distributed throughout the body, with each module capable of up to 20 W heat exchange. By changing the direction and magnitude of the current flowing into the TEM, fine control of heating or cooling of each individual module can be achieved. To achieve conductive heat exchange with the body, each TEM heats or cools a small sac (~50 mL) of water held against the skin. The custom software developed for the TCS can, for each TEM, either maintain a constant TEM temperature or, alternately, vary TEM temperature to maintain a constant skin or core temperature. The TEMs are held in place using a webbing system that permits multiple configurations and maximal flexibility in the placement of the TEMs. Overall, the TCS will permit fine and flexible control of overall and regional body temperature not possible with previous systems. Initial unmanned validation work has successfully proven the concept of heating/cooling control using TEMs by manipulating the temperature of insulated bodies of water. Present work revolves around the validation of the TCS on human subjects.

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## ASSESSMENT IN HUMANS OF HEAT EXCHANGE AT SPECIFIC BODY AREAS USING A MULTI-COMPARTMENT LIQUID COOLING/WARMING GARMENT

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Assessment of maximal heat exchange between different body areas and the environment is important for the purpose of designing more effective protective clothing systems against extreme ambient temperatures. For this purpose, we developed a multi-compartment liquid cooling/warming garment (LCWG) with the capability to impose simultaneously different temperature regimes in various compartments. Six healthy men ages 25-35 served as subjects in these studies. The experimental design consisted of sequentially cooling ( $8^{\circ}\text{C}$ ) and warming ( $45^{\circ}\text{C}$ ) selected body zones via LCWG inlet water temperature while maintaining the remainder of the garment's body zones at  $33^{\circ}\text{C}$ . The same zones also were studied at more moderate LCWG water temperatures ( $15^{\circ}\text{C}$ ,  $28^{\circ}\text{C}$  and  $38^{\circ}\text{C}$ ) as reference points for establishing relationships between LCWG surface temperature and capability of body heat exchange. The quantity of heat exchange with the LCWG from highest to lowest was sleeveless shirt, shorts, sleeves, and hood, likely related to differences in the size of the anatomical areas covered by the various compartments and thus involved in the heat exchange process. The hands under gloves cooled to  $8^{\circ}\text{C}$  released approximately 1.0kcal/min and under heating to  $45^{\circ}\text{C}$  absorbed approximately 0.7-0.9kcal/min, which was less than for the zones mentioned above. For the different regions of the upper extremities, the order of effectiveness of heat exchange was forearms, shoulders, and hands. However, considering heat transfer from the LCWG in relation to tubing length, these results confirm our prior research demonstrating that the hands have a high capability to transfer heat in and out of the body. The finding of individual variability in quantity of heat exchange from different body regions and different temperature conditions on the skin surface suggests that advanced protective garments for extreme environments including outer space can be enhanced by obtaining individual thermal profiles and incorporating these data in garment design. This should help provide a safer, more economical, comfortable, and effective garment for physical performance in harsh environments.

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## ABSENCE OF BAROREFLEX MODULATION OF SKIN SYMPATHETIC NERVE

### ACTIVITY AND SWEAT RATE DURING WHOLE-BODY HEATING IN HUMANS

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Baroreflex control of skin blood flow during heating is well documented, but the effects of baroreceptor loading/unloading on sweating are less clear. Therefore, this project tested the hypothesis that pharmacologically induced alterations in blood pressure in heated humans would lead to baroreflex mediated changes in skin sympathetic nerve activity and sweat rate. In seven subjects, and under normothermic and heat stress conditions, mean arterial blood pressure was first reduced (~10 mmHg) and then increased (~15 mmHg) via bolus infusions of 100 µg sodium nitroprusside followed by 150 µg phenylephrine. These drugs were infused through a catheter inserted into an antecubital vein. Bolus phenylephrine administration began approximately 60 seconds after the onset of nitroprusside infusion. In both normothermic and heat stress conditions the following responses were monitored: sublingual and mean skin temperatures, heart rate, beat-by-beat blood pressure (Colin), skin blood flow (laser-Doppler flowmetry), local sweat rate (capacitance hygrometry), and skin sympathetic nerve activity (microneurography from peroneal nerve). Whole-body heating increased skin and sublingual temperatures, heart rate, cutaneous blood flow, sweat rate, and skin sympathetic nerve activity, but did not change arterial blood pressure. During whole-body heating, heart rate was significantly elevated during sodium nitroprusside-induced reductions in blood pressure (74 ± 4 to 92 ± 4 bpm; P<0.001) and significantly reduced during phenylephrine-induced elevations in blood pressure (92 ± 4 to 68 ± 4 bpm; P<0.001), thereby demonstrating appropriate baroreflex function in these subjects. Skin sympathetic nerve activity was not affected by pharmacologically induced alterations in blood pressure regardless of the thermal condition. Similarly, sweat rate was not attenuated when blood pressure was reduced during whole-body heating. To eliminate the possibility that the lack baroreflex modulation of skin sympathetic nerve activity and sweat rate was due to rapid and transient changes in blood pressure, in four subjects steady state intravenous infusions of sodium nitroprusside (20 to 60 µg • kg<sup>-1</sup> • min<sup>-1</sup>) were administered over a period of 8-12 minutes. Steady-state decreases in mean arterial blood pressure of ~10 mmHg caused baroreflex-mediated increases in heart rate (~20 bpm) but did not change skin sympathetic nerve activity during normothermia. Furthermore, during the heat stress steady-state reductions in mean arterial blood pressure did not significantly change skin sympathetic nerve activity or sweat rate. These results indicate that the lack of change in sweat rate and skin sympathetic nerve activity observed during bolus infusions of vasoactive drugs was not due to the short time period in which blood pressure was altered. Taken together, these data suggest that skin sympathetic nerve activity and sweat rate are not modulated by arterial baroreflexes in normothermic or moderately heated individuals.

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## FACTORS AFFECTING TISSUE FREEZING

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Low air temperatures and high wind speeds are associated with an increased risk of freezing exposed skin. Siple and Passel (1945) derived their wind chill index (WCI) from cooling experiments on a water-filled cylinder. In addition, they exposed bare skin to different climates and observed at what combinations of air speed (v) and temperature, and thus WCI, skin freezing occurred. They reported that an increased risk of frostbite was prevalent at a WCI above 1400 kcal/(m<sup>2</sup>·h) (1628 W/m<sup>2</sup>). Later conducted experiments on finger freezing showed that skin freezing rarely occurred at WCI values below 1400; values above this were often, but not always, associated with skin freezing. These results have been re-examined (Danielsson, 1996). It was found that the WCI underestimated the convective heat transfer coefficient ( $h_c$ ). Therefore, new risk curves were developed based on a corrected convection equation valid for body parts in a cross air flow ( $h_{C0} v^{0,62}$ ) and finger frostbite data presented in the literature. An analysis of the data revealed a relationship between the frequency of finger frostbite and the surface temperature. This relation closely follows a normal distribution of finger freezing temperatures, with a standard deviation of 1°C. As the skin surface temperature falls from -4,8°C to -7,8°C the risk of frostbite increases from 5% to 95%. However, finger frostbite at considerably lower WCI values than 1400 has also been reported but these exposures were associated with snow in the air or with the skin wetted. The experience that frostbite rarely occurs in spite of high WCI-values in Antarctic during summertime have been explained by presence of solar radiation. The effects of sunshine and a wetted skin on the cooling rate can be included in the prediction equations describing the frostbite risk. The results confirm that wet skin can cause tissue freezing at a considerably lowered WCI-value, meaning e.g. that the risk changes from 43% (dry skin) to 86% (wet skin) at a temperature of -15°C and an air speed of 6,8 m/s. Calculations show also that solar radiation may prevent the skin from reaching harmful temperatures. If the sky is clear and the sun altitude is 10°, the risk of frostbite is roughly 15% compared with 50% at no solar radiation if the temperature and air speed is -15°C and 9 m/s, respectively. At a sun altitude of 40°, the risk of frostbite is negligible according to estimations. Based on the prediction model, extended risk curves have been developed, now also taking considerations in solar radiation and skin wetness. The effect of acclimation on the risk of tissue freezing, reported in the literature, has also been included as a comparison.

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## PHARMACOLOGICAL ASSESSMENT OF THE ROLE OF NITRIC OXIDE IN MOUSE MODELS OF MALARIA *IN VIVO*

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Malaria (*Plasmodium*) infections in mice share many similarities with human malaria and are common laboratory models of the human disease. However, a major species difference is the development of hypothermia, not fever, in murine malaria. Nitric oxide (NO) is implicated in the immune response and the pathophysiology associated with malaria. We have evidence of increased NO production in blood and other tissues of malarial mice, but its value to the host is unclear. In order to understand better the role(s) of NO, a pharmacological investigation was conducted to determine whether increased concentrations of NO *in vivo* have (1) an antimalarial action and/or (2) a hypothermic effect. Male MF1 mice were inoculated intravenously (i.v.) with mouse erythrocytes parasitised by *P. berghei* or *P. chabaudi* on day 0; controls received uninfected erythrocytes. Plasma NO was measured, by Griess assay of nitrites following nitrate reductase treatment, as plasma total nitrite concentrations (PTNC). Plasma was prepared from heparinised blood collected by cardiac puncture under terminal general anaesthesia produced by inhalation of diethyl ether. *P. berghei* produced a rapid, high parasitaemia following an unsustained rise in PTNC, necessitating humane killing on day 4 or 5. *P. chabaudi* produced a self-limiting parasitaemia, which was cleared in association with sustained high PTNC. Six putative NO inducers and three NO donors were tested for their ability to increase PTNC in uninfected mice, the most effective agents then being evaluated for their ability to decrease morbidity caused by *P. berghei*. Lipopolysaccharide (LPS, *Salmonella abortus equi*) was the most effective inducer, as indicated by PTNC 3 h after subcutaneous (s.c.) injection: 0.9% saline (10 ml/kg)  $6 \pm SD 5$  nmol/ml; LPS (0.5 mg/kg)  $85 \pm 46$  nmol/ml,  $P < 0.01$ ; LPS (4 mg/kg)  $119 \pm 60$  nmol/ml,  $P < 0.001$ , all groups  $n = 6$ ). Increases in PTNC induced by LPS were associated with falls in colonic temperature (minus  $\sim 1.5^\circ C$ ). S-Nitrosoglutathione (SNOG, 16.8 mg/kg s.c.) was the most effective NO donor *in vivo*, elevating PTNC for at least 90 min, but having no effect on temperature. LPS (4 mg/kg, once daily) and SNOG (16.8 mg/kg, twice daily) were injected s.c. in *P. berghei* infected mice on days 1, 2 and 3. LPS, but not SNOG, increased PTNC (control  $43 \pm 24$  nmol/ml; LPS  $89 \pm 37$  nmol/ml,  $P < 0.05$ ,  $n = 7$ ), splenomegaly and survival (on days 4, 5 and 6), whilst decreasing parasitaemia and hypothermia compared with infected mice receiving vehicle (4% dimethyl sulfoxide in olive oil, 10 ml/kg). Two NO synthase inhibitors, aminoguanidine hydrochloride (AG) and S-(2-aminoethyl)isothiourea dihydrobromide (100 and 200 mg/kg intraperitoneal injection, i.p.) were evaluated for their ability to reduce the rise in PTNC induced by LPS (0.5 mg/kg i.v.) in uninfected mice. AG proved more effective and was tested for its ability to compromise the natural resolution of *P. chabaudi*. AG (200 mg/kg i.p. once daily on days 5 – 13) inhibited the *P. chabaudi* induced rise in PTNC (day 14 PTNC: 0.9% saline  $61 \pm 40$  nmol/ml, AG  $5 \pm 4$  nmol/ml,  $P < 0.05$ ,  $n = 5$ ) and increased morbidity, but had no effect on parasitaemia or hypothermia measured on alternate days from day 0 to day 28. In summary, no consistent relationship was evident between the ability of the pharmacological agents used here to modify NO activity *in vivo*, monitored as PTNC, and their effects on malaria parasitaemia and colonic temperature in mice.

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**PERINATAL ENERGY REGULATION OF STRUTHIONIFORMES – A COMPARATIVE  
STUDY OF THE NORTH ISLAND BROWN KIWI (*APTERYX MANTELLI*)**

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Birds vary to a great extend in their mode of development (e. g. altricial, precocial). Already at the time of hatching there are clear morphological and behavioural differences. This draws the attention to the phase of the embryos development inside the egg and causes the question if there are general differences in the energy budgets of bird embryos and freshly hatched chicks. In general, the large variety of egg sizes, energy contents of the eggs and the incubation times may result in different energy demands for development. It is still debated whether or not there are obvious differences between the various bird orders. Comparisons on energy deposit (spare yolk) and metabolic rate during pre- and postnatal stages may give useful insights between different developmental strategies. So, a lot of screening data are needed to clarify the basic aspects of perinatal energetics. Therefore we investigated a wide spectrum of different bird species of several orders (measured under identical experimental conditions and methods). Amongst other bird species, we worked on the Struthioniformes (ostrich *Struthio camelus*, rhea *Rhea americana*, emu *Dromaius novaehollandiae*, North Island brown kiwi *Apteryx mantelli*). They represent the largest living birds, they lay the biggest eggs and they show a very slow embryonic development (especially the kiwi has the second longest incubation time known in birds, which amount to 75-85 days). Their hatchlings are highly precocial. These outstanding characteristics make it highly interesting to look at the embryological and postnatal development of these birds with regard to the question if either the developmental parameters of the struthioniformes follow a special course or they resemble those of "normal" birds - and thus support the view of a general basic course (independent of mode of development and egg mass) more or less valid for all birds. Based on our results we found that the Struthioniformes exhibit many extraordinary characteristics in their eggs and in their incubation physiology, departing from expected values. Nevertheless, the basic parameters such as the general occurrence of a plateau phase (including relative timing and length) and the merely facultative occurrence of an internal pipping are within the normal range expected for birds in general. This also applies to the total sum of energy turnover rate during embryogeny. The high amount of spare yolk thus can serve the chick as an exclusive source of energy and material for tissue production (kiwi: 17 days).

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## ACTIVITY OF HEPATIC PYRUVATE KINASE AND PEPCK IN FASTED RATS DURING THE ACCLIMATION TO HYPERTHERMIC ENVIRONMENT

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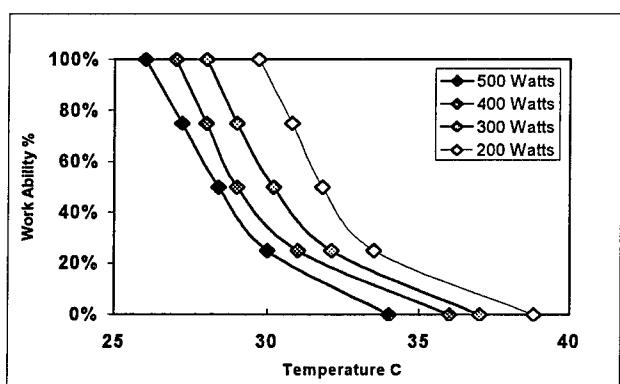
The goal of this work has been to observe the effect of acclimation to hyperthermic environment on the activity of hepatic pyruvate kinase (PK) and phosphoenolpyruvate carboxykinase (PEPCK) and liver glycogen content in 4 days fasted rats. Adult white Wistar female rats were used for this experiment. The experiment was conducted on four day-fasted rats. The experimental animals were divided into 6 groups (fasted rats - 0+4, 3+4, 10+4, 17+4, 26+4 and 56+4 days) depending on the time of the exposure to heated environment. Control groups were kept at room temperature ( $20\pm2$  °C). The heat-acclimation was performed in special heated chamber with regulated temperature of  $35\pm1$  °C and air humidity of 20-30%. Animals were narcotized with ether narcosis. Liver pieces were frozen in liquid nitrogen. In fasted rats, the activity of hepatic PEPCK and glycogen content are significantly decreased regardless of duration of exposition to high environmental temperature. These positive correlation with time of exposition is proved with significant coefficient ( $r=-0.798$  for glycogen content and  $r=-0.904$  for PEPCK). During acclimation to heat temperature, the PK activity are increased ( $r=0.845$ ). The reduced glycogen content is associated with declining of the PEPCK activity ( $r=0.620$ ) and increasing of the PK activity ( $r=-0.614$ ). In whole experimental period, the multiplicative regressive analyses show significant dependence between changes in activity of PK and PEPCK ( $r=-0.749$ ). The decreased activity of hepatic PEPCK and liver glycogen content and the increased activity of PK in fasting conditions, imply that in heat-acclimated rats processes of gluconeogenesis are decreased and glycolysis are increased.

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## HEAT STRESS AND ABILITY TO WORK IN THE CONTEXT OF CLIMATE CHANGE

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Work environments which are too hot do not just affect comfort, but are a real concern for health protection, and for the ability of workers to perform tasks associated with their work. High temperatures have been found to be associated with lower work productivity, increased accident frequency and reduced motor task performance. This study investigated the likely effect of increasing temperature as a result of climate change, on work productivity, using as a framework the international standard for work in hot environments (ISO7243, 1989). The results are based entirely on modeling work, using the functions provided in this report. The international standard for work in hot environments identifies maximum Wet Bulb Globe Temperatures (WBGT) for continuous work (8 hours per day) and interrupted work (for example 75% work with 25% rest), beyond which a worker is at risk of heat exhaustion. These values are given for metabolic rates ranging from 120 to 340 Wm<sup>-2</sup> (ISO7243, 1989). WBGT values as low as 22.5°C can result in restrictions of the "time allowed for work", or the "work ability" for un-acclimatised people. For people who are acclimatized to hot environments, such restrictions on work time begin at about 26°C (WBGT). We accept that the WBGT index of heat exposure is "comfort-based". Nevertheless, it is used to manage heat exposure by restricting the time of work in heat. A model of the relationship between WBGT and "work ability" was created from the international standard functions. The reduction of work ability per °C increase is substantial in the range of 26-33°C: 20-30%. The modelling results are shown in the Figure below.



The Inter-governmental Panel on Climate Change suggest that temperature increases in this century will be within the range of 1.4-5.8°C (IPCC, 2001). Further, the future temperature increase is likely to vary greatly by region and season. A 1°C increase in global temperature may result in increases of several degrees during the hottest months of the year in certain parts of the world. We calculated the impact on "work ability" in a population, and put the reduction indicated by the model above into a context of "preventable burden of disease".

In this case, "disease" was defined as the reduction of "work ability". It was considered that a reduction of the ability to work, and do normal household chores due to heat, would have a similar impact on "health" as a temporary disability from clinical disease (e.g. malaria fever). A 1°C increase in temperature for two months may contribute up to 10% of the total preventable "burden of disease". These results have potentially serious consequences for the economic conditions of populations in relation to predicted climate change, particularly in tropical regions.

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## POSTNATAL ONTOGENY OF THERMOGENESIS IN ADELIE PENGUIN CHICKS

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Marine birds critically depend on their reproduction colony on land for breeding. For most avian species in the Antarctic area, the breeding period is restricted to the short summer period. Unfledged hatched Adélie penguin chicks (*Pygoscelis adeliae*) are successively brooded by their parents until they are able to maintain their own body temperature. This strategy will immobilize one of the parents on the colony while the successful growth of the chicks depends on feeding by both parents. The rapid ontogeny of thermoregulatory mechanisms and metabolic pathways is therefore of critical importance for optimizing chick growth and survival and parental energy investment under harsh climatic conditions. Postnatal ontogeny of thermogenesis and metabolic pathways was therefore investigated in Adélie penguin chicks (Dumont d'Urville station, Terre Adélie, Antarctica). Chicks from identified nests were used in one-day experiments in the lab to assess thermoregulatory function and then put back on the colony. Newly hatched chicks showed small though significant regulatory thermogenesis (indirect calorimetry) but rapidly became hypothermic. The lower critical temperature (LCT) was around 32 degrees C and thermal conductance was high ( $8.0 \text{ W m}^{-2} \text{ degree C}^{-1}$ ). By 2 weeks of age, peak metabolic rate was markedly increased (2-fold when expressed per unit weight and 8 fold per animal) while LCT was slightly shifted downward to 18 degree C. By one month of age, emancipated chicks showed marked capacity for cold resistance mainly through an improved thermal insulation illustrated by a very low LCT (-17 degree C) and low thermal conductance ( $2.2 \text{ W m}^{-2} \text{ degree C}^{-1}$ ). Peak metabolic rate could not be attained. Regulatory thermogenesis closely depended on shivering (assessed by accelerometry), which was visible soon after hatching. Thermogenic efficiency of shivering was rather low at birth but increased with age. Special authorisation was obtained to kill a few chicks of known age (decapitation after halothane anaesthesia) to investigate the ontogeny of tissue metabolic pathways. In newly hatched chicks, the activity of most enzymes was higher in leg (gastrocnemius) than in trunk skeletal muscles (pectoralis). Growth was associated with marked rises in the activity of most metabolic pathways. Improvement in thermogenic capacity paralleled marked increases in skeletal muscle oxidative capacity (cytochrome oxidase, citrate synthase), lipid metabolism (3-hydroxyacylCoA dehydrogenase, carnitine palmitoyl transferase) and carbohydrate metabolism (hexokinase, pyruvate kinase). These results therefore indicate that thermal emancipation of Adélie penguin chicks may be determined primarily by thermal insulation after thermogenic and metabolic processes have improved. The rapid maturation of insulative, thermogenic and metabolic processes may contribute to the breeding success of the species.

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## THERMOREGULATION IN FEMALE EMPEROR PENGUINS

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Breeding emperor penguins (*Aptenodytes forsteri*) must face the drastic antarctic winter while fasting. Efficient thermoregulation is therefore a key parameter for survival. Exhaustive investigation on thermoregulation and thermogenic mechanisms of adult emperor penguins has not yet been performed despite earlier studies (Pinshow et al., 1976; Le Maho et al., 1976). The aim of this work was therefore to study the thermoregulatory function of emperor penguins from the breeding colony of Pointe Géologie (Terre Adélie, Antarctica). During winter, nine females weighing around 30 kg were caught and used in one-day laboratory investigations at the Dumont d'Urville station. Non employed females (because of limited number of males) were used to limit the impact of the study on reproduction. Energy expenditure at various ambient temperatures ranging from 10 to -40 degrees C was measured by indirect calorimetry in a thermostated chamber and body as well as skin temperatures was continuously monitored with thermocouples. Shivering activity was assessed by accelerometry. Parameters were recorded and analysed with a computerised acquisition system. Resting metabolic rate remained constant between 10 and -10 degrees C (thermoneutral zone, TNZ) at  $2.04 \pm 0.05 \text{ W kg}^{-1}$  and increased linearly from -20 degrees C. At -40 degrees C it was 49% above that measured in the TNZ. Lower critical temperature was  $-16.4 \pm 2.8 \text{ degrees C}$ . Thermal conductance was  $1.26 \text{ W m}^{-2} \text{ degree C}^{-1}$ . Body temperature ( $37.2 \pm 0.2 \text{ degrees C}$ ) was constant over the range of ambient temperatures used. Skin temperatures (back, abdomen and flipper) gradually decreased as ambient temperature dropped indicating peripheral vasoconstriction to limit heat losses but were maintained above a few degrees C. Skin temperature of the feet remained at the highest level possibly because of postural adjustment. Respiratory quotient was close to 0.7 indicating a major use of lipids as fuel substrate. Shivering appeared between -20 and -30 degrees C and estimated tremor activity was increased 2 fold at -40 degrees C. Shivering threshold temperature was -24 degrees C indicating the existence of small capacities for regulatory nonshivering thermogenesis corresponding to +15% of the resting metabolic rate in the TNZ. Present results therefore indicate that body size and shape as well as insulative and metabolic adaptations to cold contribute to the efficient thermoregulation of adult emperor penguins.

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## EXPRESSION OF AN AVIAN UNCOUPLING PROTEIN IN GROWING MUSCOVY DUCKLINGS

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In mammals, it is known that body temperature and energy balance are regulated by modulation of the proton electrochemical gradient across the inner mitochondrial membrane through an uncoupling protein (UCP), which promotes the dissipation of oxidation energy in brown adipose tissue. Since then, UCP homologues have been characterised in other tissues and a number of animal and plant species suggesting larger physiological roles of these mitochondrial proteins than previously anticipated. Very recently, we have identified a complementary DNA from chicken (*Gallus gallus*) that encodes an avian UCP (avUCP; Raimbault et al., 2001). The predicted amino-acid sequence of avUCP, deduced from the nucleotide sequence is 55, 70, 70 and 46% identical to mammalian UCP1, UCP2, UCP3, and plant UCP, respectively. AvUCP may be involved in facultative thermogenesis because it is up regulated in avian models of cold-induced regulatory nonshivering thermogenesis (cold-acclimated ducklings) and diet-induced thermogenesis (inefficient line of chickens). We analysed the expression of avUCP in growing male Muscovy ducklings (*Cairina moschata* L.) reared at either thermoneutrality (25 degree C) or in the cold (4 degree C) from 1 wk of age. Ducklings were obtained from a commercial stockbreeder (Ets Grimaud, France). They were fed ad libitum with a commercial mash and had free access to water. Tissues were obtained after birds were killed by decapitation and stored at -80°C until analysis. Tissue total RNA was extracted with standard method. Analysis of avUCP messenger RNA in duckling tissues using RT-PCR and Northern blots, revealed a 1.8 kilobase transcript uniquely present in skeletal muscle. The pattern of expression of avUCP is similar to that of the mammalian UCP3, which is predominantly expressed in skeletal muscles. It however differs from that of the ubiquitous UCP2. Relative abundance of avUCP mRNA differed between skeletal muscles and depended on fibre typing. Relative abundance changed with age between hatching and 5 weeks of age and was affected by chronic cold exposure. These results therefore indicate that avUCP expression is modulated by age, ambient temperature and may possibly be involved in the modulation of oxidative metabolism, thermogenesis and energy balance in birds. By analogy with results in other species, the precise role of avUCP may not be exclusively in thermogenesis and further studies are required to clarify this important issue in avian energetics.

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## FOREARM TISSUE TEMPERATURE AND THE CIVD RESPONSE

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Recent work suggests an influence of the mean body skin (Tsk) and deep body temperatures (Tb) on the characteristics of the cold-induced vasodilatation (CIVD) response. Briefly, both the minimum (Tfi,min) and the maximum finger temperature (Tfi,max) during CIVD were higher when Tb was elevated, and the onset time of the CIVD response was reduced at higher Tsk. The question remains, however, about the influence of the forearm tissue temperature on the CIVD response for a given Tsk and Tb. On two different occasions, eleven healthy male subjects pre-conditioned their forearm tissue at two different water temperatures, 20 and 38°C, until steady state forearm muscle temperature was achieved. Following the conditioning period (129 ± 15 and 85 ± 15 min for 20 and 38°C, respectively), the fingers of the conditioned forearm were immersed in a 5°C bath for 30 min to study the characteristics of the CIVD response. During the finger immersion, Tsk and Tb were not different between the two conditions (Tsk = 34.3 ± 0.6°C, Tb = 36.8 ± 0.2°C), but the temperature 3cm deep into the forearm's *flexor digitorum profundus* muscle was different (p < 0.05), averaging 23.6 ± 1.7°C and 36.7 ± 0.6°C for the 20 and 38°C conditions, respectively. The arterial blood temperature in the radial artery measured at the wrist level averaged 28.2 ± 2.5 and 35.6 ± 0.9°C for the 20 and 38°C conditions, respectively (p < 0.05). The two forearm conditions caused significant differences in all the CIVD parameters during the 30 min immersion in 5°C water as shown in the Table.

CIVD parameters	Pre-conditioning conditions (mean ± SD)	
	20°C	38°C
Tfi,average (°C)	6.2 ± 0.9	8.3 ± 1.6*
Tfi,max (°C)	7.0 ± 1.1	9.8 ± 1.6*
Tfi,min (°C))	5.0 ± 0.1	5.6 ± 0.3*
Onset Time (min)	7.8 ± 1.4	5.2 ± 0.5*
Peak Time (min)	11.7 ± 5.2	5.9 ± 2.7*
Amplitude (°C)	2.1 ± 1.0	4.4 ± 1.6*

Tfi,average: mean finger temperature from the 5th to 30th minute of immersion

Tfi,max: maximal finger temperature during the first CIVD phase

Tfi,min: minimum finger temperature before the first CIVD phase

Onset Time: time from immersion to Tfi,min

Peak Time: time from Tfi,min to Tfi,max

Amplitude: difference between Tfi,max and Tfi,min \* p < 0.05

It was concluded that a low forearm tissue temperature impedes the CIVD response despite normal Tsk and Tb, possibly by decreasing the temperature of the arterial blood to the fingers.

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## A 36-HOUR COMPARISON OF CORE TEMPERATURE AT REST AND DURING EXERCISE USING RECTAL PROBE AND PILL TELEMETRY

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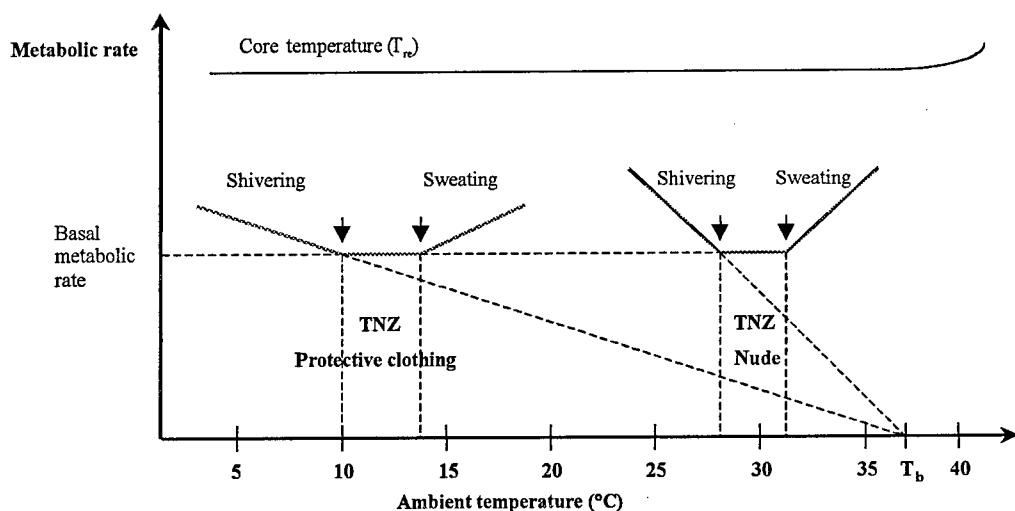
Long-term measurement of core temperature in unrestrained humans is being made possible by recent development of pill telemetry technology. The technology, however, has been previously validated only over a short time period ranging from 1 to 3 hours. Since the mobility of the pill in the GI tract has been identified to change the absolute temperature of the pill and its temperature response characteristics, it is essential to validate the technology for a longer time period if the pill telemetry is to be used for several hours. Eleven non heat-acclimatized males volunteered to participate in two 36-hour sleep deprivation studies where their core temperature was continuously monitored using a rectal probe inserted 15 cm beyond the anal sphincter, and a pill telemetry ingested at the beginning of each study. The data were collected about 40 min after the ingestion of the pill using small data loggers attached to the subjects. The subjects, dressed with shorts and T-shirt, rested in an environmental chamber maintained at 30°C and 50% relative humidity for the duration of the studies. On 3 occasions during each study and separated by a 12-hour interval, the subjects exercised on a treadmill for 2 hours to elevate their core temperature to about 39°C. The subjects walked at 5.6 km/h with a 7-14% grade or ran at 8.8 km/h on the level. The temperature of all ingested fluid was controlled at 37°C to minimize any drink-induced effects on core temperature, particularly on the temperature readings from the pill telemetry. During the resting periods over the 36-hour studies, there was no statistical difference ( $p = 0.065$ ) between the rectal probe ( $37.45 \pm 0.20^\circ\text{C}$ ) and the pill telemetry ( $37.4 \pm 0.24^\circ\text{C}$ ) readings, the absolute difference averaging  $0.12 \pm 0.09^\circ\text{C}$ . This absolute temperature difference was similar between the first hour of data collection ( $0.15 \pm 0.11^\circ\text{C}$ ) and the 36<sup>th</sup> hour of data collection ( $0.15 \pm 0.14^\circ\text{C}$ ). These results do not support an effect of the mobility of the pill in the GI tract on the temperature difference with the rectal temperature readings. By the end of the exercise sessions, the subjects were hyperthermic with a core temperature averaging  $38.96 \pm 0.40^\circ\text{C}$ . On average during the exercise sessions, there was a statistical difference ( $p < 0.05$ ) between the rectal probe ( $38.51 \pm 0.24^\circ\text{C}$ ) and the pill telemetry ( $38.39 \pm 0.25^\circ\text{C}$ ) readings, the absolute difference averaging  $0.24 \pm 0.10^\circ\text{C}$ . This absolute difference was significantly larger than the one observed during the rest periods ( $p < 0.05$ ). It was concluded that during rest periods, the pill telemetry is able to estimate core temperature as well as a rectal probe for the whole transit time of the pill in the GI tract ( $> \sim 24$  hours). During exercise, however, a low GI perfusion could be responsible for a temperature lag.

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## THE THERMONEUTRAL ZONE WHEN WEARING AIRCREW PROTECTIVE CLOTHING

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Heat stress can be a significant problem for pilots wearing protective clothing during flights because such clothing limits evaporative heat loss, which may produce fatigue and impair performance. The thermal loads in the cockpit environment and wearing a survival suit both influences the thermal stress experienced by the user. It was therefore of interest to determine the thermoneutral zone (TNZ) in subjects wearing aircrew protective clothing. In nude, resting subjects TNZ has been determined to lie between 28 and 30°C ambient temperature ( $T_a$ ) (Gagge *et al.* 1967). The thermoneutral zone when wearing protective clothing has not previously been determined. We hypothesized that wearing protective clothing will affect heat exchange with the surroundings and cause displacement of the TNZ. Eight volunteer subjects participated in two randomized series of tests. In series A they dressed as they normally do for flights, (including helmet, two layers of underwear, and an uninsulated survival suit), in series B they only wore shorts. In both series heart rate, rectal and 13 skin temperatures, metabolic heat production and subjective evaluation of thermal sensation and thermal comfort were measured during one-hour exposure. In series A they were exposed to five different ambient conditions; 0, 10, 14, 18, and 25°C respectively. In series B they were exposed to seven different ambient conditions; 15, 20, 25, 28, 31, 35, and 40°C respectively. In agreement with the findings of Gagge *et al.* (1967) the criteria for thermoneutrality in nude subjects (series B) were fulfilled in the temperature range of 28-31°C. The TNZ was displaced downwards in subjects wearing protective clothing (series A) to an ambient temperature range of 10 to 14°C, where physiological parameters were lowest, with mean skin temperature at 33.6-34.1°C and  $VO_2$  at  $0.33 \pm 0.05 \text{ l} \cdot \text{min}^{-2}$ , and subjects were comfortable. Wearing aircrew protective clothing causes a displacement of the TNZ from 28-31°C ( $T_a$ ) (nude subjects) to 10-14°C ( $T_a$ ). The results of this study can be used as a guideline for regulation of cockpit temperature when wearing protective clothing.



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## **THERMAL PROTECTION OF THE FETAL SHEEP IS ROBUST UNDER FIELD CONDITIONS**

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When body temperatures of maternal and fetal sheep are recorded in the laboratory over the last 2 months of pregnancy, fetal body temperature closely follows that of the mother, resulting in a very stable feto-maternal gradient within each pair (Laburn *et al.*, 1992). Furthermore, the nychthemeral rhythm of temperature shows an amplitude of approximately 1°C. Recent advances in the use of miniature data loggers to make continuous recordings of body temperatures have enabled us to extend our measurements of fetal temperature to natural field conditions. At approximately 110 days of gestation (term approximately 150 days), and under halothane general anaesthesia and sterile surgical conditions, data loggers (StowAway and TidBit, Onset, Massachusetts, USA) were implanted into the abdominal cavities of 4 pregnant sheep, and one fetus in each sheep. Body temperatures then were recorded every 5 minutes. After surgery, maternal and fetal body temperatures were recorded for 1-2 weeks in the laboratory, after which the pregnant ewes were sent out into the field where recordings continued throughout birth and for 4 weeks post partum. Air temperature in the laboratory was  $\pm$  23°C, and there was no wind, while air temperature in the field ranged between 10 and 23°C. Body temperature recordings in the laboratory concurred with previous findings, in that the feto-maternal gradient stayed constant for each mother-fetus pair at between 0.3 and 0.7°C, and daily indoor body temperatures of both mother and fetus fluctuated very little (amplitude of less than 1°C). Under natural field conditions maternal body temperatures showed daily rhythms with a nychthemeral amplitude of up to 3°C, but fetal temperatures fluctuated much less (up to 1°C). The fetus was protected against precipitous falls in maternal body temperatures at night. Consequently, the feto-maternal gradient varied significantly more than in laboratory conditions. After birth, lamb temperatures stayed 0.5 – 1.0°C higher than that of their mothers for the first month. Thus field experiments demonstrate thermal protection of the fetus to be more robust than would be expected from laboratory studies.

Laburn, H.P., Mitchell, D. & Goelst, K. (1992) Fetal and maternal body temperatures measured by radiotelemetry in near-term sheep during thermal stress. *Journal of Applied Physiology*, 72, 894-900.

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## PREGNANCY IMPAIRS CENTRAL PROSTAGLANDIN RELEASE AND THE FEBRILE RESPONSE TO INTRAVENOUS IL-1 $\beta$ IN RATS

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Rats have an attenuated febrile response to exogenous and endogenous pyrogen near the term of pregnancy. The present experiments were carried out on 12 nonpregnant and 12 pregnant Sprague-Dawley rats to test the hypothesis that pregnancy impairs the release of E series prostaglandins (PGE's) into the interstitial fluid of the organum vasculosum laminae terminalis (OVLT) following intravenous administration of recombinant rat interleukin-1beta (rrIL-1 $\beta$ ). Interstitial fluid of the OVLT was sampled in chronically-instrumented, conscious rats by microdialysis and PGE's were determined by radioimmunoassay. Basal OVLT PGE's were similar in nonpregnant and pregnant rats. Intravenous administration of rrIL-1 $\beta$  produced significant increases in OVLT PGE's and core temperature in nonpregnant rats. In near-term pregnant rats, however, neither OVLT PGE's nor core temperature increased significantly following I.V. administration of rrIL-1 $\beta$ . Intravenous administration of vehicle did not significantly alter OVLT PGE's or core temperature in either group of rats. Thus, our data support the hypothesis that pregnancy impairs the release of PGE's into the interstitial fluid of the OVLT following intravenous administration of rrIL-1 $\beta$ . Perhaps rrIL-1 $\beta$  does not elicit a normal end-mediator response because there is an alteration in the number or properties of cytokine receptors near the term of pregnancy, or, alternatively, there may be increases in the circulating levels of IL-1 receptor antagonist in rats as there is in humans near the term of pregnancy. These possibilities warrant further investigation.

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## ACUTE RESPONSES OF HEAT ACCLIMATISED CYCLISTS TO INTERMITTENT SPRINTS IN TEMPERATE AND WARM CONDITIONS

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The performance and the acute physiological responses of heat acclimatised cyclists were measured during intermittent sprints in temperate and warm conditions. While the effects of heat on submaximal exercise have been well studied, there are few reports of its effects on intermittent high intensity exercise. Performance has variously been unaffected (Falk et al., 1998) improved (Ball et al., 1999), or decreased (Maxwell et al., 1999) in the heat. Furthermore, none of these studies involved heat acclimatised subjects. Accordingly, ten heat acclimatised cyclists (mean  $\pm$  standard deviation age  $34 \pm 6$  yr; body mass  $73.4 \pm 7.0$  kg;  $\dot{V}O_{2\text{peak}} 52.8 \pm 5.8 \text{ ml kg}^{-1} \text{ min}^{-1}$ ) were recruited from a Darwin cycling club. An initial familiarisation session was conducted during which subjects pedalled the ergometer at the approximate test intensities. Steady state submaximal  $\dot{V}O_2$  and  $\dot{V}O_{2\text{peak}}$  were measured during a subsequent visit. During the final two visits the experimental treatments were conducted. Treatments consisted of 3 sets of  $5 \times 20$  s cycling sprints followed by a sprint to voluntary exhaustion (TTE). Temperate conditions were  $20.2 \pm 0.4$  °C;  $46 \pm 2$  % humidity,  $108.5 \pm 1.4$  kPa water vapour pressure and warm conditions  $30.5 \pm 0.4$  °C;  $47 \pm 10$  % humidity,  $206.8 \pm 6.4$  kPa water vapour pressure and were administered in a randomised order. Oxygen consumption was greater in the warm condition ( $p=0.02$ ), pulmonary ventilation was greater in the TTE sprint only ( $p=0.00$ ), and heart rates were greater in the warm condition ( $p=0.02$ ). Blood lactate and respiratory exchange ratios were not significantly different between conditions. Subjects lost  $2.1 \pm 0.2$  % of body mass in the warm condition and their time to exhaustion in the final sprint was  $50 \pm 13$  s in the warm condition compared with  $60 \pm 7$  s for the temperate condition ( $p=0.02$ ). We conclude that the elevated oxygen consumption reported for submaximal exercise in the heat also occurs during high intensity intermittent exercise for heat acclimatised athletes. There was no evidence of the increased reliance on anaerobic metabolism that has been reported for sub maximal exercise in the heat. The mild level of hypohydration induced by 3 sets of 20 s sprints in 30 °C heat may be sufficient to limit the time to exhaustion of a subsequent sprint.

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## PREDICTING THE USEFULNESS OF COLD GAS BREATHING FOR REDUCING HEAT LOAD DURING WARM WATER DIVING

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With military diving operations in the warm waters of the Middle East as well as commercial diving operations in nuclear reactor coolant pools and contaminated water, the problems of heat stress in diving have become a concern. This paper explores the utility of manipulating the density, specific heat, and inspired gas temperature of the breathing mixture to increase respiratory heat loss ( $H_{Resp}$ ) and reduce heat load during extended diving missions in warm water. In the absence of a specific study investigating  $H_{Resp}$  during warm water diving conditions, data from several sources in the open scientific literature were used to predict  $H_{Resp}$  during shallow warm water diving conditions. Oxygen consumption ( $\dot{V}O_2$ ) and minute ventilation ( $\dot{V}E$ ) were obtained for US Navy divers performing underwater bicycle exercise in 34.4 °C while breathing air from a demand regulator at 20 fsw (Doubt and Dukta, 1990). Body heat production was determined by converting  $\dot{V}O_2$  to Watts and subtracting the external work. Predictions of  $H_{Resp}$  were calculated for warm (31 °C) and cold (1 °C) air, normoxic helium (heliox), and normoxic SF6 gas mixtures while at rest and during light (50 W) and moderate (105 W) underwater exercise. Respiratory heat loss for breathing heliox at the two inspired gas temperatures was derived using the linear regression equations of  $H_{Resp}$  versus  $\dot{V}E$  described by Hoke *et al.*, (1976). These heliox data were then scaled using data from Webb (1970) on  $H_{Resp}$  for gas mixtures with different density  $\times$  specific heat products to provide  $H_{Resp}$  values for air and the normoxic SF6 gas mixture. All calculations of  $H_{Resp}$  assume that 1) the inspired gas is dry, 2) the expired gas is fully saturated with water vapor, and 3) conductive heat losses are negligible. Results showed that  $H_{Resp}$  ranged from 12 to 40 W at rest, 44 to 80 W during light exercise, and 75 to 120 W during moderate exercise. When expressed as a percentage of total body heat production,  $H_{Resp}$  ranged from 8 to 23% at rest, 14 to 22% during light exercise, and 14 to 20% during moderate exercise. The  $H_{Resp}$  values reveal that increasing the convective character of the gas mixture results in only a minor benefit for reducing body heat load during shallow warm water diving. Furthermore, the data predict that switching from warm to cold gas breathing will reduce body heat load by an additional 10 to 15% during resting conditions, but that the benefit of cold gas breathing will diminish as work load increases. These findings likely reflect the fact that  $H_{Resp}$  for dives at or near surface pressure is predominantly dependent upon evaporative cooling (Hoke *et al.*, 1976). Experiments are currently planned to test these predictions.

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## EVIDENCE FOR THE INVOLVEMENT OF EICOSANOIDS IN REGULATION OF NORMAL BODY TEMPERATURE

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A regulated rise in the thermoregulatory set point has been postulated to be responsible for both fever and circadian elevation of body temperature ( $T_b$ ). Consequently, in view of the fever-inducing role of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), it was suggested that this rise could be prostaglandin-dependent. In support of this are data demonstrating that the normal nighttime rise in  $T_b$  of rats can be prevented by antipyretic drugs known as cyclooxygenase inhibitors (Scales & Kluger, 1987). However, circadian changes in hypothalamic PGE<sub>2</sub> production have not yet been established. We have recently shown that 5-lipoxygenase (Paul *et al.*, 1999; Fraifeld *et al.*, 2000) and cytochrome P-450 (Kozak *et al.*, 1998; 2000) pathways of arachidonate metabolism are involved in the process of endogenous antipyresis (cryogenesis) during response to endotoxin. Whether lipoxygenase- and epoxygenase-derived eicosanoids are also involved in the regulation of normal  $T_b$  is unknown. The experiments were carried out on conscious young adult male CD-1 mice and Sprague-Dawley rats maintained at 12:12-h light/dark photoperiods.  $T_b$  was recorded either biotelemetrically or by using a rectal probe. PGE<sub>2</sub> production by *ex-vivo* incubated hypothalamus was measured before and after the onset of dark. The hypothalami were excised after decapitation. The inhibitors of different metabolic pathways of arachidonic acid cascade were injected intraperitoneally (ip). Intra-abdominal implantation of temperature-sensitive transmitters and intracerebral implantation of a guide cannula were performed in mice anaesthetized with ketamine (80 mg/kg, ip) and xylazine (16 mg/kg, ip). It was found that (i) dark-induced elevation in  $T_b$  of mice and rats was accompanied by a significant increase in hypothalamic PGE<sub>2</sub> production (by 71 and 60%, respectively); (ii) indomethacin at a dose (5 mg/kg, ip) that did not affect the daytime values of  $T_b$ , prevented the increase in  $T_b$  after the onset of dark; (iii) the  $T_b$  of CD-1 mice tended to decrease during the light period, reaching the minimum values between 12:00 to 14:00. This decrease was significantly reduced by pretreatment of mice with the inhibitor of leukotriene (LT) synthesis MK-886 (1 mg/kg, ip); (iv) injection of 0.3 nmol LTC<sub>4</sub> into the lateral ventricle, which caused a drop in  $T_b$  of CD-1 mice by ~1.6 °C during the light phase, significantly reduced the nighttime rise in  $T_b$ . The results presented support a role of PGE<sub>2</sub> and leukotrienes in the regulation of normal daily variations of  $T_b$ , which occurs in a similar fashion as during fever.

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## ESTROGEN RAISES THE SWEATING THRESHOLD IN POSTMENOPAUSAL WOMEN WITH HOT FLASHES

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Hot flashes (HFs) are the most common symptom of menopause and consist of profuse sweating, peripheral vasodilation, and sensations of intense heat. Recent research has shown that HFs are triggered by small fluctuations in  $T_c$  acting within a reduced thermoneutral zone. Although estrogen ameliorates HFs in most symptomatic women, its mechanism of action is not known. Here we sought to determine if estrogen reduces  $T_c$  fluctuations and/or raises the sweating threshold in postmenopausal women with frequent HFs. Twenty women were randomly assigned to receive 17 $\beta$ -estradiol (1 mg/day, p.o.) or placebo for 90 days. Before treatment they had  $T_c$  (rectal) and  $T_{sk}$  (4 weighted sites) recorded in a 26°C, 50% RH room for 3 hours. Data were sampled every 15 sec by computer.  $T_c$  fluctuations were estimated by computing the standard deviation (SD) for each subject's 3 hr recording. On a separate day the  $T_c$  and  $T_{sk}$  thresholds for sternal sweating (capacitance hygrometry) were measured using 42°C circulating water pads on the legs and torso. HFs were recorded for 2 weeks in diaries. After treatment all procedures were repeated. Data were analyzed with 2-way repeated measures ANOVAs and are shown in the Table.

		Estrogen	Placebo
$T_c$ (mean $\pm$ SD)	Pre	37.9°C $\pm$ .2	37.9°C $\pm$ .2
	Post	38.0°C $\pm$ .3	37.9°C $\pm$ .2
$T_{sk}$ (mean $\pm$ SD)	Pre	34.0°C $\pm$ .4	34.0°C $\pm$ .5
	Post	34.1°C $\pm$ .5	34.3°C $\pm$ .6
$T_c$ Swt.Th. (mean $\pm$ SD)	Pre	37.9°C $\pm$ .3	38.0°C $\pm$ .2
	Post	38.1°C $\pm$ .2*	37.8°C $\pm$ .4
$T_{sk}$ Swt.Th. (mean $\pm$ SD)	Pre	36.2°C $\pm$ 1.0	35.8°C $\pm$ .7
	Post	35.9°C $\pm$ .4	36.2°C $\pm$ .8
HFs/day (mean $\pm$ SD)	Pre	7.9 $\pm$ 2.6	8.3 $\pm$ 5.4
	Post	2.3 $\pm$ 1.9**	5.7 $\pm$ 3.3

\*p < .05 Pre vs. Post; \*\*p < .001 Pre vs. Post

Mean  $T_c$  and  $T_{sk}$  did not significantly change in either group nor did the SD of  $T_c$  (estimate of  $T_c$  fluctuations). Estrogen significantly raised the  $T_c$  sweating threshold and reduced HF frequency in the treated group but not the placebo group. We conclude that estrogen therapy ameliorates HFs by raising the  $T_c$  sweating threshold, but does not affect  $T_c$  fluctuations.

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## A YEAR IN THE THERMAL LIFE OF A HERD OF SPRINGBOK (*Antidorcas marsupialis*)

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The springbok, a small southern African antelope, maintains arterial blood temperature within narrow daily limits ( $\sim 1$  °C), despite being subjected to high thermal loads in summer, often with concomitant water stress. The key to their homeothermy is thought to lie in thermoregulatory behaviour and the low radiant absorptance of their pelage. The pelage, however, also is thin with a high conductance and springbok are reported to be susceptible to hypothermia during cold winter months. As a consequence of technical limitations, there are no quantitative data on seasonal variations in body core temperature in springbok nor, indeed, in any other antelope. We used miniature data loggers to measure body core temperature in springbok, undisturbed in their natural habitat, for one year. We implanted data loggers (mass 30 g) into the abdomen of seven (2 male, 5 female) springbok (body mass 20-35 kg), during halothane (1-2%) general anaesthesia (duration 6 min). After surgery, springbok were released into a fenced 62 ha enclosure, where they ranged freely with other species of African ungulates. Body temperatures were recorded continuously, every 30 min, to an accuracy of 0.04 °C, and hourly-measurements of microclimate data were obtained from a weather station at the study site. After 12-14 months, springbok were recaptured (using nets) and loggers were removed under anaesthesia. Over the year, the animals were subjected to air temperatures that fluctuated between -6 °C and +34 °C, and a nycthemeral range of globe temperature that exceeded 40 °C. Daily body temperature exhibited a small amplitude nycthemeral rhythm (mean  $1.2 \pm 0.2$  °C) varying, on average, between 38.8 °C and 40.0 °C, with a temperature peak at 18:30 and a trough in the early morning between 05:00 and 07:30. In all seven animals, mean daily body temperature was linearly correlated with mean daily air temperature ( $P < 0.0001$ ) so that, on average, body temperature increased 0.02 °C per 1 °C increase of air temperature. There also was a positive linear relationship between minimum daily body temperature and minimum air temperature, but the relationship between peak body temperature and maximum air temperature was less robust, particularly in the male springbok. Analysis of seasonal patterns also revealed that mean daily body temperature was significantly higher in summer months (Oct to Jan) than in mid-winter (June to July), by  $\sim 0.3$  °C. Both the minimum and peak body temperature were significantly lower in winter months, so that the nycthemeral amplitude of body temperature, on average, was the same during all months. Thus, during hotter summer months, there was no demonstration of adaptive heterothermy, a thermal adaptation thought to be characteristic of antelope in arid or semi-arid regions. Also, although body temperature patterns were correlated with environmental thermal loads, the circadian and circannual variation of body temperature was small, a finding that we believe supports the idea of the importance of behavioural modifications in maintaining the stability of internal temperature.

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## TYMPANIC TEMPERATURE DURING THE EXPOSURE TO ELECTROMAGNETIC FIELDS EMITTED BY CELLULAR PHONE-PART II: EXPERIMENTS ON MEN

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For hand-held radiotelephones used by the general public, International Commission on Non-Ionizing Radiation Protection (ICNIRP) recommends that the localized SAR in the head be limited to 2 W/kg averaged to 10 g tissue in the head. This limit protects telephone users from the thermal effect of the radiation, but temperature rise, even when it is within the admissible range, may cause physiological effects. However, the problem has not been clarified yet. The aim of the experiment was to assess the temperature changes during exposure to EMF emitted by mobile phones. Before attempting to determine the effect of mobile phone EMF exposure on the tympanic temperature (T<sub>ty</sub>), we made sure that the tympanic thermometer met the EMC (electromagnetic compatibility) requirements, i.e. its operation was not disturbed by mobile phone EMF, provided that T<sub>ty</sub> was measured in the ear at the side of the head opposite that to which the telephone was applied. In order to explain if materials with dielectric properties similar to those of the biological material are heated during the exposure to EMF, we conducted a phantom experiment. The experiment was performed using the container with dimensions corresponding roughly to the dimensions of the human head. The container was filled with 0.9% NaCl. Exposure time was 60 min. Before the exposure, mean temperature of the saline was 23.14±0.04°C, while after the exposure it was 23.38±0.10°C, and the difference was statistically significant, p<0.000001. The second step of experiment was performed in seven young men, aged 19-29 (mean age 23.3±5.3) years, who were examined twice: on a day without exposure (C) and on a day with continuous exposure (E) to cellular phone EMF for 60 min at 900 MHz, SAR 1.23W/kg. Written consent was obtained from each of the participants prior to starting the experiment. The test was performed in the laboratory under controlled conditions. From 6 to 7 the subjects were examined by a physician, and were subjected to the resting ECG with heart rate variability analysis. From 7 to 8 p.m. the subjects used cellular phone. The subjects were not informed which day was (E) and which (C). From 8 p.m. till 11 p.m. the subjects listened to music. During the experiment the arterial blood pressure (BP), heart rate (HR) and T<sub>ty</sub> were monitored. This paper is limited to data on the tympanic temperature. T<sub>ty</sub> was measured every 10 sec by a thermistor probe (ST-21S, sensor Technica Co.) attached to the tympanic membrane from about 6.30 p.m. to 11 p.m. We compared T<sub>ty</sub> during the day (E) and day (C) separately for 2 periods: (1) 7-8 p.m., (2) 8-11 p.m. using Wilcoxon matched-pairs signed-ranks test, for each subject and for the whole group Mean T<sub>ty</sub> during (1) and (2) differed significantly between day (E) and (C) (p=0.0000). The analysis of T<sub>ty</sub> of each subject revealed individual variations. Further investigations are being performed to explain these differences.

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## EFFECT OF IMMOBILIZATION STRESS ON THE FUNCTION OF UNCOUPLING PROTEIN-1 IN RAT BROWN ADIPOSE TISSUE

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Brown adipose tissue (BAT) is the major site of nonshivering thermogenesis (NST). The BAT-specific mitochondrial protein, uncoupling protein-1 (UCP-1) is the key molecule in NST in this tissue, and the amount and activity of UCP-1 change according to the physiological requirements for thermogenesis in BAT. It has been shown that chronic nonthermal stress, that is, repetitive immobilization, improves the cold tolerance through an enhanced NST in the stressed rats. Furthermore, the removal of interscapular BAT led to a loss of improved cold tolerance and significant reduction of NST in the stressed rats. These findings suggest that such cross adaptation between cold and nonthermal stress may be caused by, at least in part, stimulation of BAT thermogenic function. However, whether UCP-1 is involved in the functional activation of BAT thermogenesis in the nonthermal stressed rats remains unknown. To answer this question, we determined both the amount and activity of UCP-1 in BAT of the stressed rats. Male Wistar rats were subjected to either acute (3 hours) or chronic (3 hours/day for 4 weeks) immobilization stress by being immobilized with wire mesh on a wooden board. We measured GDP binding and expression of mRNA and protein as index of UCP-1 activity and amount, respectively. In acute group, we measured above parameters immediately after 3 hours immobilization. In the chronic stress groups, we measured in both the resting stage (24 hours after last immobilization stress) and the stressing stage (0 hour after last immobilization stress). After the rats were sacrificed by decapitation, interscapular BAT were excised quickly. Mitochondria were isolated for GDP binding experiment and Western blot analysis, total RNA were prepared for Northern blot analysis. Immobilization stress increased GDP binding in both of acute and chronic groups, but the increment in GDP binding from resting to stressing stage was significantly enhanced in the chronic groups than in the acute stress group. UCP-1 expression (both mRNA and protein) only increased in the chronic groups. These results indicate that repetitive immobilization stress can enhance thermogenic capacity through increasing both of amount and activity of UCP-1 in BAT. It is thus suggested that repetitive immobilization stress would endow with cross adaptation to cold through an increased function of UCP-1.

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## NEUROPHARMACOLOGICAL BASIS OF HYPOTHALAMIC INTERACTION OF THERMO- AND OSMOREGULATORY SIGNALS: INTEGRATIVE ROLE OF THE MEDIAN PREOPTIC NUCLEUS

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The hypothalamus contains nuclei/regions involved in the perception and integration of systemic and central signals important for body temperature homeostasis. Thermosensory function resides in preoptic hypothalamic regions like the medial preoptic area (MPA) and the median preoptic nucleus (MnPO). The organum vasculosum laminae terminalis (OVLT) outside the blood-brain barrier is identified as initiating the fever response to circulating cytokines. Pyrogenic factors either directly contact OVLT neurons or indirectly activate anterior hypothalamic structures *via* stimulation of cyclooxygenase-2 (COX-2) in their vascular endothelium or induction of endothelial or neuronal nitric oxide synthase (eNOS, nNOS) with formation of nitric oxide (NO). Neurons in the posterio-lateral hypothalamus (LHA) are involved in energy balance linked to metabolic cold defense, and MPA neurons control thermoregulatory effectors. According to expression patterns of immediate-early-genes (*c-fos*), both mild heat acclimation (33°C, 48 h) and heat stress (39°C, 1 h) reveal distinct and differential activation of neurons in the MPA, MnPO, septum and LHA, whereas mild dehydration (24 h) causes neuronal stimulation in the magnocellular paraventricular (mPVN) and supraoptic nucleus (SON), subfornical organ (SFO) and MnPO. Using microtranssection, transsynaptic viral as well as classical neuronal tracing techniques, the parvocellular PVN and MnPO can be regarded as integrative structures for afferent signals of various autonomic control circuits. A myriad of potential neurotransmitters has been discussed to convey thermosensory signals and facilitate neuronal integration. Recently, the NO-system has evolved as a major key player in hypothalamic control of thermoregulation and is discussed in detail, based on physiological and histochemical approaches. Nitrergic neurons are densely concentrated in the PVN, SON, OVLT, SFO, MPA and MnPO as revealed by nNOS mRNA *in situ* hybridization, immuno- and enzyme cytochemistry as well as Western blotting. Heat acclimation, heat stress and endotoxin-induced fever are accompanied by enhanced nNOS activity and partially also nNOS mRNA expression in the MPA, MnPO and LHA but not PVN, SON or SFO. Central application of NO donor substances stimulates cutaneous and vascular heat defense reactions in rats and rabbits. Central enzymatic blockade of nNOS by subtype-specific inhibitors reduces endurance, elevates threshold temperatures for salivation and tail skin vasodilation, and finally leads to a rise in core temperature under conditions of heat stress in eu- and/or dehydrated rats. In addition, dehydration and angiotensin II (AngII) stimulated drinking is reduced. Congruent results can be obtained after central suppression of nNOS mRNA expression employing long-term icv infusion of nNOS mRNA antisense deoxynucleotides. As indicated by Fos immunostaining, osmoregulatory signals (dehydration, AngII) preferentially activate nitrergic neurons within the MnPO, whereas heat stimuli induce *c-fos* expression in cells possibly representing direct targets of neuronally released NO. Complex interneuronal wiring appears therefore to underly the NO-mediated thermoregulatory heat defense and replenishment of extracellular fluid volume under conditions of high environmental temperature.

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## POSTALIMENTARY HYPERTERMIA: A ROLE FOR GASTROINTESTINAL BUT NOT FOR CALORIC SIGNALS

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Fasting causes suppression of metabolic rate (MR) and core temperature ( $T_c$ ). In contrast, food intake induces immediate elevation of MR and  $T_c$  (postalimentary hyperthermia, or thermic effect of food, TEF). These are not simply changes due to altered energy reserves, instead they are regulatory changes since, e.g., acute cold exposure can increase MR even in the state of severe fasting hypometabolism (Székely *et al.*, 1997). The question regarding the nature of information channels for such regulatory changes has not been resolved. In the present studies MR and  $T_c$  of Wistar rats were measured (by diaferometer and thermocouples, respectively) at thermoneutrality following a 48-h food withdrawal or in connection of re-feeding. Spontaneous re-feeding for 3-h with rat-chow or saccharine-sweetened  $\text{CaCO}_3$  was followed by MR and  $T_c$  measurements. In other cases, during MR and  $T_c$  measurements, artificial re-feeding was performed: a) through a preimplanted gastric cannula either calorie-rich (FWG) or calorie-free (HD) substance was injected (water in controls), b) through a preimplanted jugular cannula either 4 ml 40% glucose or 2.5 ml 20% fat emulsion (Intralipid) (or 0.9% NaCl in controls) was infused within 2-h. All implantations were performed under intraperitoneal ketamine + xylazine (78 + 13 mg/kg) anesthesia 3-7 days before fasting, and all operated animals were given a narcotic overdose after finishing the measurements. Fasting caused suppression of MR and  $T_c$ . Spontaneous re-feeding was followed by reversal of this suppression both in chow- and  $\text{CaCO}_3$ -fed rats; not the composition but the volume of ingested substance seemed to be important. Both FWG and HD injections elicited elevations in MR and  $T_c$ , although the dynamics were different for the two substances (the rise commenced earlier in case FWG was given). Neither glucose, nor Intralipid infusion modified low MR and  $T_c$  values of fasting rats. It is concluded that not caloric signals, neither oro-facial neural impulses, rather gastrointestinal signals (most likely due to stretch, nutrients, gastrointestinal hormones) may be responsible for the postalimentary rise in MR and  $T_c$ , and probably similar (or inverse) gastrointestinal signals may be detectable in the background of the fasting-induced hypometabolism and hypothermia.

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## SHIVERING THERMOGENESIS IN AUSTRALIAN ANTARCTIC EXPEDITIONERS: COMPARISON OF THERMOREGULATORY MODELS

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The general response to acute cold stress is vasoconstriction and increased heat production (M) via shivering. Both skin and internal body temperatures ( $T_c$ ) must be lower than a fixed threshold before shivering ( $\Delta M = M - M_{\text{basal}}$ ) occurs. Several thermoregulatory models include  $\Delta M$  algorithms as a  $f(T_c, \bar{T}_{sk})$ . Other models include  $\Delta M$  as a  $f(\% \text{ body fat} (\%BF), \text{ lean body mass (LBM)})$ . We examined how well 3 models predict  $\Delta M$  for a given cold stress in a data set of resting women and men prior to their sojourn for a year in Antarctica. Six women and 29 men (%BF ranges 10-46%) resting semi-supine, unclothed except for underwear + smock ( $R_T = 0.022 \text{ m}^2 \cdot \text{K} \cdot \text{W}^{-1}$ ), were exposed for 2 h to cold air. Fifteen men and 5 women completed a cold stress test (CST group:  $T_a = 5.7 \pm 0.6 \text{ SD } ^\circ\text{C}; rh = 50\%; V = 0.2 \text{ m} \cdot \text{s}^{-1}$ ) and a separate group of 14 men and 1 woman completed a cool test (Cool group:  $T_a = 8.4 \pm 1.3 \text{ SD } ^\circ\text{C}$ ). Extensive peripheral ( $\bar{T}_{sk}$  and finger temperatures) vasoconstriction occurred during the CST and less so in the Cool, elevating mean resting temperature pill level ( $T_c$ ) by  $+0.15-0.2^\circ\text{C}$  for the first 30min followed by a mean decline in  $T_c$  of  $-0.01^\circ\text{C}/\text{min}$ .  $\Delta M (\text{W} \cdot \text{m}^{-2})$  at 5 time points was compared against 3 model predictions: (1) Tikuisis and Giesbrecht (Tik-G), 1999:  $\Delta M = 156 \cdot (37 - T_c) + 47 \cdot (33 - \bar{T}_{sk}) - 1.57 \cdot (33 - \bar{T}_{sk})^2 \cdot \%BF^{-0.5}$ ; (2) Stolwijk and Hardy (S-H), 1977:  $\Delta M = [13 \cdot (T_c - 37) + 0.4 \cdot (\bar{T}_{sk} - 34)] \cdot (\bar{T}_{sk} - 34)$  and (3) Tikuisis et al., (Tik), 1991:  $\Delta M/\text{LBM} = \{0.0422 \cdot (35.4 - \bar{T}_{sk})^2\} / (\%BF)^{0.506}$ . Root mean square deviation (RMS) comparing  $\Delta M$  vs each model output is shown in the Table.

Data vs Model	$RMS (\text{W} \cdot \text{m}^{-2})$	$RMS (\text{W} \cdot \text{m}^{-2})$	$RMS (\text{W} \cdot \text{m}^{-2})$
	Men (N=14)	Men (N=15)	Women (N=5)
obs $\Delta M$ vs Tik-G	28.4 $\pm$ 8.2	26.6 $\pm$ 13.2**	29.6 $\pm$ 15.1
	Cool group	CST group	CST group
obs $\Delta M$ vs S-H	23.2 $\pm$ 16.3	34.9 $\pm$ 14.1**	33.8 $\pm$ 15.6
	Cool group	CST group	CST group
obs $\Delta M$ vs Tik †	23.7 $\pm$ 15.7	22.9 $\pm$ 9.3	15.2 $\pm$ 3.1
	Cool group	CST group	CST group

[\*\*RMS Comparison between models  $P < 0.0001$ ; all others NS. †Normalized to  $\text{W} \cdot \text{m}^{-2}$ . No women in Cool group]. RMS from the Tik-G was < than the S-H prediction in the CST group of men. All predictions were equal in RMS in the Cool groups. For  $\%BF \leq 20\%$ , Tik-G was highly correlated with integrated mean body temperature ( $T_{b,I}$ ) derived from partitional calorimetry ( $R^2 = 0.89$ ;  $P < 0.001$ ;  $\Delta M(\text{Tik-G}) = -33.5 \cdot (T_{b,I}) + 1226$ ).  $\Delta M$  calculated from cold-air models incorporating  $\%BF$ ,  $T_c$  and  $\bar{T}_{sk}$  inputs serve as reliable predictors of shivering response over a limited cold stress for both men or women.

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## LIMITS TO PHYSICAL PERFORMANCE UNDER BOTH HOT AND COLD THERMAL EXTREMES

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It is well established that physical performance is hindered under both extreme hot and extreme cold thermal conditions. The physiological factors limiting performance in either environment will depend on the subjects' training status, as well as type, duration and intensity of exercise. Recent evidence in trained subjects indicates that endurance performance in hot and very cold environments is closely linked to critically high or low body temperature, respectively. In opposition to this hypothesis of a critical level of body temperature, there are reports indicating that some subjects fatigue during light exercise in extreme hot and cold conditions with body temperatures of  $\sim 37\text{-}38^{\circ}\text{C}$ . Therefore, exhaustion in extreme environments should be conceived as a complex phenomenon most likely resulting from the interaction of body temperature, as well as metabolic and circulatory factors. Nevertheless, there will be exercise conditions where one of these variables will be the most important. For instance, during prolonged exercise in hot environments, trained cyclists have been found to rapidly fatigue at strikingly similar body temperature ( $\sim 40^{\circ}\text{C}$ ), when its initial value (36.0, 37.4 or  $38.4^{\circ}\text{C}$ ) and rate of rise (0.10 vs.  $0.05^{\circ}\text{C}/\text{min}$ ) are systematically manipulated. This volitional fatigue (i.e., inability to sustain the same workload) can be acutely reversed by perfusing the skin with cold water. Conversely, during prolonged exercise in the cold with continuous exposure to rain and wind, some people fatigue when reaching a critical level of hypothermia ( $\sim 35^{\circ}\text{C}$ ). Together, these findings suggest a pivotal role of body temperature on the etiology of fatigue in trained people. Critically high or low temperature could directly alter the function of vital organs such as the brain and heart (e.g. diminishing central command and cardiac contractility, respectively) or indirectly impair tissue circulation and metabolism. During prolonged exercise in less extreme hot environments the elevation in body temperature is accompanied by marked reductions in cardiac output, skeletal muscle blood flow and skin blood flow, and altered skeletal muscle metabolism, as indicated by the greater glycogen utilization and lactate production and declining skeletal muscle oxygen uptake at exhaustion. These metabolic alterations are accentuated during maximal exercise, encompassing significant reductions in systemic and skeletal muscle  $\text{O}_2$  delivery and uptake. During maximal exercise in hot environments, diminished skeletal muscle ATP production might instead be the main factor causing fatigue.

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## PLASMA VOLUME MEASUREMENT: COMPARISONS DURING SHORT-TERM THERMONEUTRAL AND COLD-WATER IMMERSION

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While exposure to short-term (<2hr) water immersion elicits increases in plasma volume (PV) during thermoneutral immersion (34.5°C), and a PV decrease during cold-water immersion (18°C), the magnitude of these shifts is inconsistent. Previous data have shown that the most prevalent, indirect PV measurement technique, which utilises changes in haematocrit (Hct) and haemoglobin concentration ([Hb]), underestimates actual PV changes during thermoneutral immersion when compared to a direct, tracer-dilution technique (Evans blue (EB) dye). Such methodological comparisons have not been made during cold-water immersion, leaving our understanding of PV changes during such exposures unclear. Therefore, we compared both indirect and direct PV measures (EB dye tracer-dilution) during both thermoneutral and cold-water immersion. We also evaluated the utility of an EB dye computer programme. Seven healthy males (age 27.6 yr SD ±9.2, height 183.1 cm SD ±4.6, mass 82.1 kg SD ±9.1, skinfold thickness 83.5 mm SD ±28.0) were tested three times (60 min; balanced design): seated upright in air (control: 21.2°C SD ±1.1); thermoneutral immersion (34.5°C SD ±0.2) and cold immersion (18.6°C SD ±0.2). Posture was identical across tests, with immersion to the third intercostal space, and tests being separated by two weeks. Plasma volume was determined at immersion baseline and during the control test, using three methods (EB dye column elution; EB dye computer programme; Hct/[Hb] calculation), and during immersions using the EB dye column elution and Hct/[Hb] calculation methods. Plasma volume during the control trial remained stable, and equivalent across and between the three methods ( $P>0.05$ ). During thermoneutral immersion, PV increased by 16.2% (±1.4) and 8.5% (±0.8) when determined by the EB dye column elution method and the Hct/[Hb] calculation, respectively (both  $P<0.05$ ). The Hct/[Hb] calculation underestimated relative PV change by 43% (±9.1;  $P<0.05$ ), when compared with the EB dye column elution method. During cold immersion, PV decreased significantly (17.9% ±3.0 (EB dye) and 8.0% ±1.2 (Hct/[Hb]); both  $P<0.05$ ), with the latter representing a 52% (±6.8;  $P<0.05$ ) underestimation of PV change. When the control and pre-immersion baseline data were combined, the absolute PV, derived using the EB dye computer programme, correlated well with the EB dye column elution PV ( $r=0.83$ ;  $P<0.05$ ). The current study is the first to show that the Hct/[Hb] method clearly underestimates PV changes during both thermoneutral and cold immersion. The mechanism underlying this PV discrepancy has yet to be elucidated. Furthermore, the EB dye computer programme method provides an acceptable alternative to the EB dye column elution technique for baseline PV determination.

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## A PERIPHERAL AND CENTRAL CHOLINERGIC PATHWAY MODULATES STRESS-INDUCED HYPERTERMIA IN THE RAT EXPOSED TO AN OPEN FIELD

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Exposure to an open-field is psychologically stressful and leads to an elevation in core temperature ( $T_c$ ). We suspect that peripheral and central cholinergic pathways modulate  $T_c$  during open field exposure and other types of stress. We recently found that methyl scopolamine (MS), a peripheral muscarinic antagonist, had an antipyretic effect on stress-induced elevations in  $T_c$  caused by handling and cage-switch stress. Pyridostigmine (PYR), an inhibitor of acetylcholinesterase activity (AChE) that leads to cholinergic stimulation in peripheral tissues, should reverse the effects of MS on  $T_c$  during open field stress. Two experiments were performed to assess the role of peripheral and central cholinergic receptors in the control of open field hyperthermia. In the first experiment, we assessed the effects of MS and PYR on open field hyperthermia. Male, Sprague Dawley rats at 90 days of age were housed individually at an ambient temperature ( $T_a$ ) of 22 EC.  $T_c$  and motor activity (MA) were monitored with radiotelemetry units implanted under Nembutal anesthesia (50 mg/kg; IP) at least 10 days prior to testing. The open field chamber consisted of an illuminated Plexiglass box (61 x 61 x 61 cm) maintained at a  $T_a$  of 22 EC. Rats were dosed IP at 1200 hr with saline, 1.0 mg/kg MS, 0.1 mg/kg PYR, or a combination of MS and PYR and placed immediately inside the open field chamber for 60 min.  $T_c$  of rats injected with saline increased by 0.7 EC during open field exposure. The hyperthermic response to open field exposure was suppressed immediately by MS and enhanced by PYR.  $T_c$  increased by 0.3 EC in the MS-treated animals. The hyperthermic response in the PYR group was nearly 0.6 EC above that of rats dosed with saline. In addition, co-administration of PYR and MS led to a  $T_c$  response identical to that of rats injected with saline. In the second experiment, we assessed if a low dose of the organophosphate pesticide chlorpyrifos (CHP) would alter open field hyperthermia with and without administration of MS. CHP irreversibly inhibits AChE and leads to cholinergic stimulation in the CNS and peripheral tissues. At 900 hr the rats were gavaged with corn oil or 10 mg/kg CHP. This CHP treatment had no effect on resting  $T_c$  or MA. The rats were then dosed IP with saline or 1.0 mg/kg MS at 1200 hr and subjected to open field stress for 1 hr.  $T_c$  of the corn oil/saline group underwent a 1.2 EC increase during open field exposure, whereas  $T_c$  of the CHP/saline group was significantly attenuated. Administration of MS attenuated the open field hyperthermia of rats treated with corn oil and CHP. We expected that a low dose of CHP would have a similar effect on open field hyperthermia as did PYR. However, CHP attenuated the hyperthermic response. Overall, activation of peripheral muscarinic receptors modulates the magnitude of hyperthermia during open field exposure. CHP leads to peripheral and central cholinergic stimulation. Since CHP attenuated open field hyperthermia, it appears that central cholinergic suppresses the hyperthermic response to open field exposure.

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## THE EFFECTS OF GENDER, AGE, AND TIREDNESS ON THE IMPACT OF DRAFTS

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Draft-induced responses are determined by great variations which are related to numerous not yet sufficiently studied personal and situational influences. The present study investigates the rôle of gender, age, and tiredness on the evaluation of drafts by pooling the data from eight experiments which were performed with similar designs and procedures. Altogether 179 persons (70 women, 109 men, 18 - 68 yrs) participated in overall almost 1,000 sessions, where several individual and situational factors were documented and first analyzed for this paper. After 20 minutes in a reference climate ( $t_a$ : 22 °C,  $\bar{V}_a$ : < 0.05 m/s, RH: 40 - 60 %), the participants moved into a climatic chamber where they were exposed to drafts for at least one hour and where air velocity (0.1 - 0.4 m/s), turbulence intensity (< 20 to > 70 %), draft direction (horizontal, diagonal, vertical), frequencies (0.05, 0.4 Hz), air temperature (11 to 23 °C), and metabolic rate (< 70 to 156 W/m<sup>2</sup>) were varied. Physical activity varied between sitting in a chair, standing before a monitor while completing a tracking test, or operating an arm-ergometer at workloads corresponding to measured metabolic rates of 104, 128, and 156 W/m<sup>2</sup>. Clothing insulation was calculated for thermal neutrality. The most sensitive arms and the neck were not covered. Initially, the participants assessed their actual health state, well-being, and tiredness. Identical questionnaires were then completed every 5 minutes concerning general thermal sensation and thermal preference, as well as perception of air movements and draft-induced annoyance separately for various body parts presented in a list. Statistical analyses based on questionnaires completed during the steady state and concerned the percentages of persons who stated draft-induced annoyance, who felt 'rather cool', and preferred a higher temperature. Generalized linear models were calculated to determine the significance of individual and situational factors. Generally, perception of air movements was independent from gender, age, and tiredness. Women were significantly more often annoyed by drafts (50 vs 30 %,  $p = 0.001$ ) and felt more often 'rather cool' in general (67 vs 50 %,  $p = 0.006$ ). So, employers who provide their employees with special clothing for moderate cold workplaces shall take this in account. Five groups defined by the decades from 20 to 70 years (30 women, 28 men) revealed no effect of age on draft-induced general annoyance, or on a 'rather cool' sensation and this was confirmed by of 2 further studies, where age varied sufficiently for statistical analysis. Despite this, it must be taken in account that the elderly are physically less active in the usual situation, they then produce less metabolic heat and they are certainly more often annoyed by drafts. The percentage of persons who stated draft-induced annoyance and a 'rather cool' sensation in general was significantly higher in rather tired than in alert persons. So, tired persons must adjust their clothing accordingly if they have not the opportunity to adjust the temperature at their workplace.

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## INFLUENCE OF INCUBATION TEMPERATURE ON THERMOREGULATORIC EFFORT IN BIRD EMBRYOS

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During the early ontogeny epigenetic adaptation mechanisms occur to adapt the organism for the expected postnatal environmental conditions. These processes can be also induced by prenatally applied temperature changes. It is easily achieved in birds by changing the incubation temperature. Our investigations have shown, that in precocial birds endothermic reactions occur already during embryonic development. It is known, that birds incubated at a lower or higher temperature than normal are acclimated to cold or heat, but there is no knowledge of the influence of prenatal temperature experiences on the development of thermoregulatory mechanisms. The aim of this study is to investigate the effect of prenatal cold and warm load in comparison to a normal incubation temperature on thermoregulatory heat production (HP) in Muscovy duck embryos (*Cairina moschata*) and chicken embryos (*Gallus domesticus*). The experiments were carried out in chicken embryos between day 15 and day 24 of incubation and in embryos of the Muscovy duck between the 29th and the 37th day of incubation. The embryos were incubated until day 17 (chickens) or day 28 (ducks) at 37.5°C and later at 34.5°C (cold, first series) or at 38.5°C (warm, second series). In a third series the embryos were incubated during the whole time of embryonic development at 37.5°C (control). HP was determined by measuring oxygen consumption of each individual embryo. Simultaneously, the temperature of the allantoic fluid (Taf) was estimated. The results can be summarized as follows. Firstly, HP in cold and surprisingly also in warm incubated chicken embryos was higher than in the control group. For instance, at the day before hatching the HP of the cold incubated embryos was  $3.21 \pm 0.32$  W/kg (n=6), of the warm incubated ones it was  $2.69 \pm 0.16$  W/kg (n=10) and the control group had a HP of  $2.1 \pm 0.06$  W/kg (n=6). The values of each group investigated was significantly different ( $p < 0.05$ , student's t-test). Secondly, the day before hatching the warm incubated duck embryos show an overshooting reaction in their HP and their Taf when rewarming after a decrease of temperature (180 min, -3°C). That means, when comparing HP and Taf the time before cooling and when re-increasing ambient temperature, it is seen that these values reach higher levels when rewarming the embryo to sink nearly to the level before decreasing temperature after a couple of hours, forming a curve. This might be a sign of an increased thermoregulatory ability in the investigated avian species.

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## EFFECT OF SELECTIVE AND NON-SELECTIVE OPIOIDS ON BODY TEMPERATURE IN WARM- AND COLD-ACCLIMATED RATS

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Exposure to ambient temperatures outside the thermoneutral zone modifies energy balance in mammals. Cold ambient temperature increases the expenditure of energy, loss of heat and intake of food. In non-hibernating mammals exposed to cold for extended periods of time, defense of body temperature (T<sub>b</sub>) occurs through the adjustment of physiological processes. Chronic exposure to ambient temperatures above the thermoneutral zone requires multiple adjustments to maintain heat balance and compensate for water loss. Since the endogenous opioid system is involved in thermoregulatory controls, this study was designed to examine the response of acclimated animals to the administration of selective and non-selective opioid agonists and antagonists. T<sub>b</sub> was measured for 4 hrs post-injection in unrestrained, male S-D rats, previously exposed to a 12 hr L/12 hr D cycle and an ambient temperature of 5° ± 1°C or 32° ± 1° C for 14-17 days. Seven days prior to testing, a polyethylene cannula was implanted in the right lateral ventricle under ketamine anesthesia (75-125 mg/kg, ip). T<sub>b</sub> was monitored at the acclimation temperature during the post-injection period. Saline icv (6 µl) or sc (1 ml/kg) had no significant effect on T<sub>b</sub> in either the cold- or warm-acclimated animals. In animals acclimated to 5°C, naloxone (NLX, 1 mg/kg, sc) induced a statistically significant decrease in T<sub>b</sub>, ranging from -1.11 to -1.86°C over the 4 hr post-injection period. Morphine (MS, 10 µg/3 µl, icv) caused hypothermia during the first 45 minutes post-injection (max decrease -1.71°C) in cold-acclimated animals. T<sub>b</sub> increased during the remainder of the post-injection period. NLX pretreatment, followed by MS, enhanced the initial hypothermia, though the effect was subadditive to that of NLX alone, and blocked the late phase hyperthermia seen with MS. PL-017 (1 µg/3 µl, icv), a mu-selective agonist, induced statistically significant hyperthermia (max ΔT<sub>b</sub> 1.13 °C) in cold-acclimated rats. CTAP (1 µg/3 µl, icv) a cyclic somatostatin analog and mu receptor antagonist, had no effect of its own and in combination with PL-017, blocked the elevation in T<sub>b</sub>. In warm-acclimated rats, NLX had no effect on T<sub>b</sub>. MS elevated T<sub>b</sub> (2°C) with increases seen in both the duration and magnitude of the effect when compared to animals conditioned to 20° C. Administration of PL-017 to warm-acclimated rats caused an increase in time-independent changes in T<sub>b</sub>. The duration of the effect was also altered in a statistically significant manner. CTAP had no effect on T<sub>b</sub> alone and in combination with PL-017 blocked hyperthermia. The data suggest that acclimation modifies the response of the animals to administration of exogenous opioids.

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## ROLE OF DOPAMINE IN THE PO/AH ON THERMOREGULATION IN FREELY MOVING RATS

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The preoptic area and anterior hypothalamus (PO/AH) are the crucial brain regions involved in thermoregulation. Due to the fact that thermoregulatory responses were induced by microinjection of norepinephrine, dopamine, 5-hydroxytryptamine, and amino acids into the PO/AH, these neurotransmitters have been considered to be involved in thermoregulation in resting rats. Microdialysis can collect virtually any substance from the brain in combination with on-going behavioral changes such as exercise. We attempted to assess the role of monoamines and amino acids in the PO/AH in relation to exercise-induced changes in Tb, using an in vivo microdialysis technique. Wistar male rats (body weight, 300-350 g) were used. Body temperature (Tb) was monitored using a telemetry system (Hasegawa *et al.*, 2000). The microdialysis-HPLC methods that we used have been described previously (Yasumatsu *et al.*, 1998). A microdialysis probe was stereotactically implanted into the left lateral PO/AH under pentobarbital sodium anesthesia (40 mg/kg i.p.). Tb increase by about 1.0°C in the first 15 min of treadmill exercise (10 m/min, for 60 min), and was maintained thereafter at a steady high level possibly due to activation of the heat loss system. The levels of dopamine metabolites (3,4-dihydroxyphenylacetic acid and homovanillic acid) in the PO/AH significantly increased during exercise. However, exercise did not induce an increase in the level of either serotonergic substances or amino acids. Our data indicate that dopamine breakdown processes in the PO/AH are activated during exercise. Dopamine in the PO/AH may be involved in the heat loss mechanisms for thermoregulation when Tb rises during exercise. We further examined to clarify the effects of dopaminergic neural mechanisms on thermoregulation, by perfusion of dopamine uptake inhibitor, GBR-12935, in the PO/AH using a microdialysis technique.

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## BRAIN LOCI RELATING TO THE BODY WARM UP DURING AROUSAL FROM TORPOR IN THE HIBERNATING GOLDEN HAMSTER

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Brown adipose tissue (BAT) thermogenesis provides basal increase in body temperature during arousal from hibernation. Several brain loci relating to the regulation of BAT thermogenesis have been investigated mostly in rats, non-hibernator. Among them, in and around the retrorubral field in the rat midbrain constitutes a tonic inhibition mechanism for BAT thermogenesis (Shibata *et al.*, 1999). The similar inhibitory mechanism on BAT thermogenesis also exists in the hamster midbrain (Hashimoto *et al.*, 1999). In the present study, we investigated 1) whether this inhibitory mechanism is involved in the body temperature change of wide range during hibernation, and 2) which brain loci are involved in the facilitation of BAT thermogenesis during arousal. Experiments were performed in accordance with the guidelines of the Ethics Committee for Animal Experiments, Asahikawa Medical University. Hibernating male golden hamster (*Mesocricetus auratus*) in the cold room (5 °C, constant dark) were moved to recording room (10 ~ 12 °C), and mounted in a brain stereotaxic apparatus for small rodents according to the rat brain atlas of Paxinos and Watson with a small modification (Hashimoto *et al.*, 1999). Under local anesthesia (4% Lidocaine), head and back skin were incised along to the midline and the skull was bored for cannula insertion. Temperatures of the rectum ( $T_{REC}$ ) and interscapular BAT ( $T_{BAT}$ ) were measured with 2 thermocouples by inserting the probe 3-4 cm beyond the anus and  $T_{BAT}$  by inserting the probe between 2 BAT pads through the skin incision, and recorded every minute with computer system. These handling procedures aroused the animals from torpid state and increased their body temperature. Initial  $T_{BAT}$  and  $T_{REC}$  were 6.5 ~ 10.5 [°C] and 6.0 ~ 9.3 [°C], respectively. Experiments were terminated by over-dose urethane injection when  $T_{REC}$  reached around 15 °C, since most hibernating animals started slightly moving at around this body temperature under the present experimental conditions. Bilateral microinjection of control saline, 10 % procaine hydrochloride or 0.1 M sodium glutamate (800 nl each side) into the midbrain region were carried out while  $T_{BAT}$  and  $T_{REC}$  were measured. Stereotaxic coordinates were 1mm lateral to the midline, 2.5 mm rostral to the vertical interaural zero plane (IA0) and 1.5 ~ 4.0 mm dorsal to the horizontal IA0. Saline microinjections affected time courses of the increase in neither  $T_{BAT}$  nor  $T_{REC}$  at any loci of the midbrain. Mean time spent for 5 °C increase of  $T_{BAT}$  around 10 °C were 29.1 ~ 38.8 min (mean  $\pm$  SEM: 30.9  $\pm$  0.17 min, n=6). During this increase of  $T_{BAT}$ ,  $T_{REC}$  was increased by 1.6-1.9 °C (1.7  $\pm$  0.0 °C). The microinjection of glutamate in and around the retrorubral field (co-ordinates: 1.5~2.5 mm dorsal to IA0), or procaine around periacqueductal gray matter (3.5 ~ 4 mm), delayed both  $T_{BAT}$  and  $T_{REC}$  increases. Results suggest that these midbrain loci are involved in the mechanism of arousal from hibernation.

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## HUMAN SURFACE TO MASS RATIO AND HEAT STRESS – A CONCEPT REVISITED

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A commonly accepted view in both human and comparative physiology literature is that a high surface to mass ratio ( $A_D/M$ ) is beneficial in the heat. This is based on the concept that body surface determines heat loss capacity for dry and evaporative heat loss (together with skin temperature and sweat rate) and that body mass determines the amount of heat producing tissues. In comparisons of males and females it was observed that the average male, being bigger (lower  $A_D/M$ ) and fitter than his female counterpart, was at an advantage in heat stress due to his higher sweat capacity. However when sweat evaporation was limited, as e.g. in hot humid climates, the males could not utilize that advantage and females had lower strain due to their higher  $A_D/M$  ratio (Shapiro *et al.*, 1980). Recent work with thermal models (Havenith, 2001) was unable to reproduce such results and predicted that a large  $A_D/M$ , as in females, would be a disadvantage when working in the heat (all other factors being equal), irrespective of the climate type. Based on this, Shapiro *et al.*'s data were re-analyzed, and it was observed that due to differences in body mass the walking exercise used created a much lower metabolic heat production for the females, which may explain their results. It was decided to perform a similar experiment, but control this for metabolic heat production by using cycle ergometer exercise.

The effect of morphological factors (body surface area [ $A_D$ ], body mass and  $A_D/M$  on heat stress responses in a hot wet (HW: 35°C 80% rh) and hot dry climate (HD: 45°C, 20% rh) of equal WBGT ( $\pm 31.6^\circ\text{C}$ ) were studied in 30 (16 males, 14 females) and 25 (16 males, 9 females) subjects respectively. Subjects exercised on a reclining cycle ergometer for 60 minutes after 30 minutes rest in the heat. The workload was set at 60 Watt. Subjects varied in morphology (HD:  $A_D/M=270\pm 21\text{ cm}^2.\text{kg}^{-1}$ ;  $A_D=1.85\pm 0.21\text{m}^2$ ; mass= $69.3\pm 12.6\text{ kg}$ ,  $\dot{V}\text{O}_{2\text{max}}=3.09\pm 0.66\text{ l.min}^{-1}$ ; HW:  $A_D/M=269\pm 22\text{ cm}^2.\text{kg}^{-1}$ ;  $A_D=1.90\pm 0.20\text{m}^2$ ; mass= $72.2\pm 13.0\text{ kg}$ ,  $\dot{V}\text{O}_{2\text{max}}=3.56\pm 0.88\text{ l.min}^{-1}$ ).  $A_D/M$  was not significantly different between males and females.

The imposed heat stress elicited a large range of body core temperatures ( $T_{re}$ : HD range 37.5-39.1°C; HW range 37.5-39.0°C). The relation of heat strain ( $T_{re}$ ) to morphology was identical in both climates (positive correlation of  $T_{re}$  with  $A_D/M$ , negative with  $A_D$  and mass), giving the bigger subjects an advantage. As  $\dot{V}\text{O}_{2\text{max}}$  was not equal for all subjects, data were also analyzed by ANOVA (high versus low  $A_D$ , body mass and  $A_D/M$  groups respectively), with  $\dot{V}\text{O}_{2\text{max}}$  as covariant. Differences between high and low  $A_D/M$  remained significant, though those for  $A_D$  and body mass became less (HD:  $p=0.06$  and 0.08; HW  $p>0.25$ ). However, even after this correction, bigger subjects were at an advantage over smaller subjects in both climatic conditions. These findings contradict earlier studies but are consistent with model calculations.

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## DOES PRIOR HEAT ACCLIMATION REDUCE MYOCARDIAL INJURY AFTER ACUTE MYOCARDIAL INFARCTION?

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Previous studies have shown that acute heat stress may potentially improve myocardial tolerance to ischemia. This phenomenon was attributed to the expression of heat shock proteins that protect the cells against ischemic damage. In contrast to ischemia, there is no existing information about the effect of heat acclimation on myocardial tolerance to acute myocardial infarction (AMI). This study aimed to evaluate whether prolonged heat acclimation reduces myocardial injury after AMI. The study was approved by the Institutional Animal Ethics Committee. 30 male Sprague Dawley rats weighing 360g were divided into 2 groups: passively heat acclimated for 4 weeks in a heat chamber (34°C, 30%RH) (H, n=15), and 4 weeks of comfort conditions (25°C, 40%RH) (C, n=15). Thereafter AMI was surgically induced in both groups under general anaesthesia (xylazine 10 mg/kg and ketamine 90 mg/kg). They recovered in comfort conditions for 4 more weeks and were then sacrificed. Body weight and rectal temperature were measured at baseline and after the first 4 weeks. Following the sacrifice, transverse serial sections of the hearts were stained with Mason Trichrome and Hematoxilin Eosin for morphometric measurements that included: necrosis area, relative necrosis area, LV cavitary area, LV muscle area and average LV wall thickness. No differences were found in increase in body weight between H and C groups after 4 weeks of heat acclimation and comfort conditions (20±15g and 30±10g, respectively). Rectal temperature measured one day after the 4 weeks of acclimation/comfort period decreased by 0.6±0.5°C in group H and by only 0.17±0.5°C in group C (P<0.05). Myocardial necrosis area and myocardial relative necrosis area were lower in the H group compared with the C group (9±4mm<sup>2</sup> compared to 12.5±5mm<sup>2</sup> and 24.9±11.8% compared with 30.4±8.6%, respectively) although not significantly. LV cavitary area was lower in the H group compared with the C group (56.9±6.4mm<sup>2</sup> and 70.7±16.6mm<sup>2</sup>, respectively) but not significantly. Average wall thickness was slightly higher in group C compared with group H although not significantly (0.5±0.2mm and 0.4±0.1mm, respectively). All the animals in the C group were successfully heat acclimated. Although not significant, better LV morphometry after AMI in this group suggests that prior heat acclimation may activate mechanisms that reduce myocardial injury after AMI. Nevertheless, further studies should be done (with increased sample population) in order to establish or refute these results.

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## THE THERMAL ENVIRONMENT AND THE HUMAN THERMOREGULATION IN SIMULATED DIVING AND IN REAL DIVING INTO THE SEA

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The necessity to work in submarine environment makes evident multiple problems regarding the human organism reactivity in these special conditions. The pressure and its variations, the thermal factors, the humidity, the swimming are some of these conditions. Hence for ensuring the divers to perform this activity it is necessary to know their organism adaptation to the mentioned factors. The studies in this field are made in two stages: simulated dry or wet diving in caisson, real diving into the sea. Our study carried out in summer with 10 professional autonomous divers, young healthful men, in their training in caisson with compressed air in dry diving at the equivalent depth of 80 m (9 ATA) and at diving into the sea at 5 m (1.5 ATA), 25 m (3.5 ATA) and 40 m (5 ATA). The time of compression and decompression, of diving and return were established according to the French Diving Tables. Following indicators were assessed: air temperature and humidity in caisson and outdoor, sea water temperature, skin temperature in central and peripheral points, heart rate, body weight, thermal sensation.

In caisson the whole time of the diving with compression and decompression was 105 minutes. The subjects, dressed only in slips, were in sitting rest. Great and sudden variations of the air temperature and humidity (increases, decreases) were determined in caisson because of the air compression and decompression. During the 5 minutes of compression the temperature increased to 43-45°C and it decreased to 35-32°C during the 20 minutes at 9 ATA, to 18°C at 2.5 ATA, followed by a new increase to 20-31°C during the decompression. The relative humidity increased at 9 ATA and in decompression to 79-100%. The skin temperature increased in all points with 1.6-1.8°C to 9 ATA and it decreased with 4.5-6.8°C to 2.2 ATA. The body weight decreased during the diving with 250-1,250 g, showing a negative water balance of the organism because of the great sweat. These data show a sudden high thermal strain.

In real diving the divers wore semiwet tight suit from alveolar neoprene and air compressed bottles on their back. The diving times were: 40 minutes at 5 m and water temperature of 20°C, 24 minutes at 25 m and 10°C, 20 minutes at 40 m and 6°C. The air temperature was 20-23°C. The skin temperature decreased with: 1.6-3.2°C at 5 m, 2.5-5.1°C at 25 m, 4.4-5.8°C at 40 m. At 25 m and 40 m the divers showed the sensation of cold, at 40 m they showed also benumbings of the hand fingers. The heart rate was 120-152 beats/min at the return from the diving. The skin temperature decrease may determine the decrease of the organism activity efficiency. There is a construction of the blood vessels, which makes heavier the gaseous organism desaturation during the decompression, hence during the return from the diving. It shows also the low thermal protection of the divers' suit at the water temperature of 6-10°C, the necessity to wear suit with higher thermal protection.

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## NOCTURNAL HYPOTHERMIA IN FASTING QUAIL: EFFECT OF PHOTOPHASE

### DURATION

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Japanese quail (*Coturnix c. japonica*) react to food deprivation with shallow nocturnal hypothermia, i.e. by lowering their body temperature and metabolism beyond the normally occurring drop during the dark phase (scotophase). This drop then becomes deeper on successive nights of fasting, which suggests that the birds are able to sense the state of their energy reserves (Hohtola *et al.* 1991) and adaptively adjust the level of their body temperature. We wanted to see whether quails are able to utilize a deeper hypothermia when the dark phase is shorter and thus maintain the energetic benefits of hypothermia constant. We used intraperitoneal radiotelemetric transmitters (VM-FH ca. 3.5 grams, Mini-Mitter, Co.) for continuous measurement of body temperature and activity of quails. The transmitters were implanted under isoflurane anesthesia (4% induction, 2% maintenance). Buprenorphine was given for 24 h postoperatively and one week was allowed for recovery before actual experiments. The birds were placed in cages (40x60x40 cm) that were stacked on a metal rack and receivers were placed underneath the cages. Readings of body temperature and activity were taken once a minute. All measurements were done at 22°C. The photoperiods used were (L:D) 12:12, 16:8, and 20:4. All dark phases were symmetrical around midnight. The birds were first maintained on a photoperiod for 8-9 days, after which food (commercial poultry mash, Raisio OY, Finland) was removed for 48 h at 8.00 a.m. (light phase). After food replacement, the measurements were continued for another 4-5 days before switching to a new photoperiod. Water was always available *ad lib.* The birds were weighed at the beginning and end of each fast. The level of hypothermia did not increase with shortening of the dark phase indicating that the birds were not able to compensate for the decreased time by increasing the depth of hypothermia. The nocturnal levels of body temperature were actually slightly higher at short scotophases. Instead, the diurnal body temperature decreased with the change in photoperiod (a slight decrease on the second fast night at 16:8 L:D, a marked decrease on both nights at 20:4). Interestingly, at the shortest photoperiod, the birds reacted to food removal by an instantaneous decrease of body temperature. Whether this was a reaction to actual absence of food, or a conditioned reaction to procedures associated with experimentation cannot be resolved here. After the nocturnal drop, the diurnal level was further decreased on the following day. The body mass loss increased slightly but significantly with shortening scotophase (15.1±0.8, 17.1±0.5 and 17.5±0.5 g at 12:12, 18:6 and 20:4 L:D, respectively), confirming that the birds were able to save less energy at short scotophases as initially suggested by the lack of a temperature response. However, the mass loss was not linearly related to scotophase length, which indicates that the diurnal drops of body temperature helped in saving energy. Nocturnal hypothermia, often considered an adaptive and flexible response to food deprivation, seems to operate in a rather ballistic fashion and cannot be adjusted to allow a deeper metabolic depression at short scotophases.

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## PERCEPTION OF PERIPHERAL COOLING

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Perception of thermal stimuli is important for cognitive interpretation and behavioral action. Relations between peripheral skin temperatures and the associated perception provide useful information for assessment of climatic conditions. Mathematical models of human thermal responses often provide a distribution of temperatures across the skin surface. Accordingly, predictions may not only give results in terms of thermal stress or physiological strain, but also in terms of for example comfort sensation, acceptance, or pain sensation. The aim of the paper is to review data from several studies of cold exposure in order to examine relations between thermal and pain sensation and cooling of the extremities. *Material and methods:* Three studies of hand cooling (34 subjects) and one study of feet cooling (8 subjects) were analyzed. They comprised 60 or 90 minutes of exposure to constant cold conditions at temperatures of -25, -12, 0, 4, 7, 10 and 15 °C. Skin temperatures were measured every minute with thermistors at several different sites of hands, fingers, feet and toes. Thermal and pain sensations were rated by subjects every 10 minutes. *Results:* In average, peripheral temperatures dropped to lower values when ambient temperature became lower. For each climatic condition the individual variation was considerable. Average ratings of thermal sensation and pain showed strong correlation with peripheral temperatures. Correlation was stronger and variation was smaller the more peripheral the temperature was located. In general, skin temperatures were about 5 °C lower at fingertip or toe for the same value of thermal sensation or pain. *Conclusions:* It seems that cooling of hand and feet are quite well perceived and quantitative relations can be found between skin temperatures and thermal and pain sensation. Relations are stronger for fingers and feet indicating that these parts are the determinants of the reaction. Thermal sensation displays a more linear drop with colder skin. Pain sensation follows a power function with larger increments at lower skin temperatures. Onset of pain appears to take place at finger/toe temperatures around 15 °C. Setting limit values for hand or feet skin temperature must recognize the fact the fingers and toes may be more than 5 °C colder for the same conditions.

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## ADAPTIVE CHANGES IN BROWN ADIPOSE TISSUE IN WISTAR RATS, ZUCKER LEAN AND OBESE RATS

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Male Wistar rats, male Zucker lean and Zucker obese rats were used. All rats in each strain were allotted into three groups so that all groups contained a similar mean value of body mass; warm acclimated(W), cold acclimated(C) and deacclimated(D) group. All rats in W groups were housed in the room at  $25\pm1^{\circ}\text{C}$  for 11 weeks, all rats in C group were housed in the room at  $10\pm1^{\circ}\text{C}$  for 11 weeks and all rats in D group were housed in the room at  $25\pm1^{\circ}\text{C}$  for 2 weeks after housing at  $10\pm1^{\circ}\text{C}$  for 9 weeks. Each rat was dissected at the end of experiments. Each rat was weighed, anesthetized with ether. Inter scapular brown adipose tissue and adrenal glands were dissected. In C groups, obese rats showed smaller rate of increase in body mass than lean rats. Increase in body mass for 2 weeks of deacclimation in obese rats was smaller than that in lean rats. Masses of brown adipose tissue per body masses were greater in obese rats than Wistar and lean rats while masses of adrenal glands per body masses were smaller in obese rats than Wistar and lean rats. In all strains, masses of brown adipose tissue and adrenal gland per body masses were greater in C groups than in W groups. Masses of brown adipose tissue per body masses were slightly smaller in D groups than in C groups while masses of adrenal glands per body masses were considerably smaller in D groups than in C groups. Lipid droplet in brown adipocyte decreased in number and lipid droplets became small lobulettes by cold acclimation. These characteristics of lipid droplets were maintained after deacclimation though fusion of lipid droplets was observed. Density of lipid in brown adipocyte was greater in obese rats than those in other strains and that in lean rats was the smallest. However, morphological changes of Zucker lean and obese rats by cold acclimation and deacclimation were essentially the same as those observed in Wistar rats. During cold acclimation, a large proliferation of mitochondria accompanied by the increase in size was observed. After deacclimation, number of mitochondria decreased and lipid droplets became slightly small in number and increased in size. However size of droplet in D group was considerably smaller than that in W group. Marked weight-reducing effect in Zucker obese rats observed during cold acclimation is partly caused by greater ratio of masses of brown adipose tissue to body masses as well as proliferation of mitochondria accompanied by the increase in size in brown adipose tissue induced by cold exposure.

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## ZUCKER OBESE RATS ARE SENSITIVE TO WEIGHT-REDUCING EFFECT AND INSENSITIVE TO OREXIGENIC EFFECT BY COLD EXPOSURE

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Male Wister, male Zucker lean rats and male Zucker obese rats at 7 weeks were allotted into 2 groups. All rats in W group were kept at  $25\pm1^{\circ}\text{C}$  for 11 weeks. All rats in C group were kept at  $10\pm1^{\circ}\text{C}$  for 9 weeks. The rats in C group were allotted into following groups so that both groups had similar body mass: a cold acclimated group(C group) and deacclimated group(D group). All rats in C group were maintained at  $10\pm1^{\circ}\text{C}$  for a further 2 weeks, and all rats in D group were transferred to a  $25\pm1^{\circ}\text{C}$  environment and maintained for 2 weeks. Each rat was dissected at the end of experiments. Each rat was weighed, anesthetized with ether. Inter scapular brown adipose tissue and adrenal glands were dissected. Increase in body masses at each age was smaller in C group than in W group. In C groups, rate of increase in body masses was less in obese rats than in lean rats. After 2 weeks of deacclimation, body masses in D group in Wistar and lean rats reached closer to those in C groups while those in obese rats were lighter in D group than in W group. The ratio of masses of brown adipose tissue per body masses were greater in obese rats than in Wistar and lean rats. While ratios of masses of adrenal glands to body masses were smaller in obese rats than in Wistar and lean rats. In Wistar and lean rats, food intake increased markedly by cold exposure while food intake in obese rats increased slightly. Oxygen intake per body mass was smaller in obese rats than Wistar and lean rats. Weight-reducing effect of cold exposure resulted from more increase in energy expenditure due to enhanced thermoregulatory thermogenesis than in energy intake. Less increase in food intake by cold acclimation in obese rats indicates they could not increase food intake in spite of enhanced thermoregulatory thermogenesis during cold exposure, because they already had maximum volume of food intake that they could eat in warm environment. Greater ratio of mass of brown adipose tissue to body mass in obese rats compared to Wistar and lean rats might be caused by hereditary nature of tendency to obesity. Smaller increase in body mass during deacclimation might be resulting from greater ratio of mass of brown adipose tissue to body mass during cold acclimation. In conclusion, marked weight-reducing effect of cold exposure observed in Zucker obese rats was caused by defect of orexigenic effect of cold exposure due to lack of leptin receptor in hypothalamus.

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## HEAT ACCLIMATION: PHENOTYPIC PLASTICITY AND CUES TO THE UNDERLYING MOLECULAR MECHANISMS

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Acclimation, in contrast to evolutionary adaptation, is a within life-time phenotypic adaptation, although it may involve a genetic basis. The phenotypic expression of heat acclimation comprises lowered metabolic rate, body temperature (T<sub>b</sub>), and heart rate, concomitantly with greater cardiovascular reserves, increased efficiency and capacity of the evaporative cooling system and elevated temperature threshold for thermal injury. Collectively these lead to an "expanded regulatory capacity" within the range of safe T<sub>b</sub>. Our current data imply that reprogrammed gene expression and changes in cellular signaling underlie the acclimatory phenomenology (Horowitz, 2001). An important adaptive feature associated with elevated threshold for thermal injury is enhanced cytoprotection. Among cytoprotective mechanisms, the inducible heat shock protein (HSP 72 kDa) was the most thoroughly studied. Acclimation leads to 200% elevation of the constitutive level of this protein, thus providing protection without the need for *de novo* HSP synthesis upon stress. Acclimation also predisposes the signaling pathway for HSP synthesis to respond faster to heat stress, at the transcription level (Maloyan *et al.*, 1999). Whether these two phenomena are interdependent is not yet understood, although other gene products follow similar pattern. There is evidence that the time window for the changes observed in the machinery of HSP induction is at the early phase of heat acclimation (1-2 acclimation days), involving accelerated excitability of the sympathetic system. The increased cardiovascular reserves constitute intrinsic changes both in the vasculature, e.g. augmented nitric oxide synthase (eNOS) level and altered G proteins function, and in the heart, e.g. altered expression of the contractile, E-C coupling and calcium regulatory proteins (Eynan *et al.*, 1998, 2000; Cohen & Horowitz, in preparation). These lead in the acclimated heart to greater pressure generation at lowered oxygen consumption, enhanced positive inotropic response and improved chamber compliance, thus matching cardiac function to greater venous return occurring upon heat acclimation. A heat acclimation-induced drop in plasma thyroxin level is responsible for many of the changes observed. An important consequence of thermal acclimation is the development of cross-tolerance between heat acclimation and impaired oxygen demands/oxygen supply balance. The beneficial implications of this feature will be discussed.

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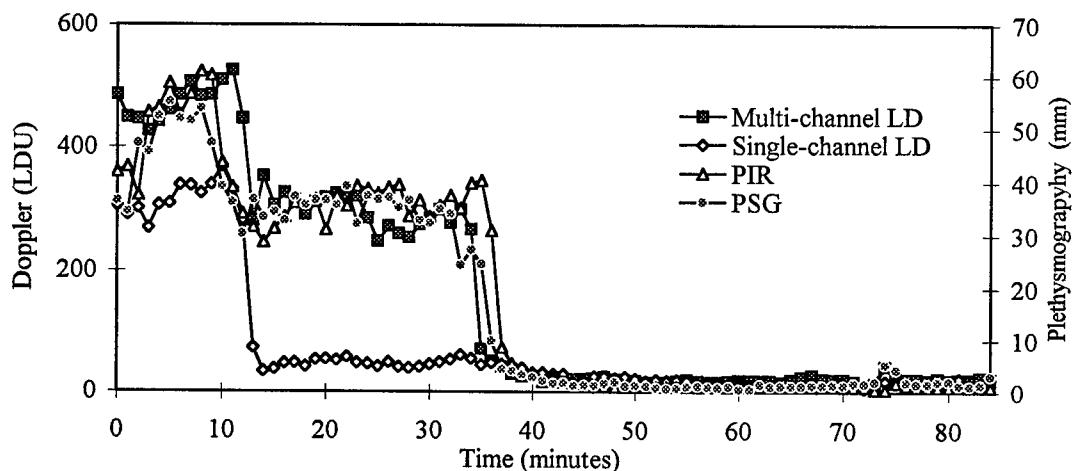
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## A COMPARISON OF FOUR TECHNIQUES FOR ASSESSING SKIN BLOOD FLOW

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Laser Doppler rheometry (LD) is widely used as an estimation of skin blood flow (SkBF). Unpublished data from this laboratory have demonstrated unexpected, and counter-intuitive LD SkBF responses. This study was undertaken to compare LD with other methods of assessing SkBF, in conditions where vasodilatation and vasoconstriction were evoked. After ethical approval, 7 medically fit volunteer subjects (6M 1F, 20-22 years) gave informed consent to participate. The subjects were immersed to chest level in a water bath (WB, initial temperature 40.6°C) with their arms at the level of the heart, and the left hand placed inside a polythene bag within a plastic box (BOX). Each finger pad of the left hand was instrumented with either, single- or multi-channel LD probes (Moors Instruments Ltd, UK), infra-red (PIR) or mercury strain gauge (PSG) plethysmography probes (Vasculab Inc, USA). When insulated auditory canal ( $t_{ac}$ ) and rectal ( $t_r$ ) temperature had increased to 38.5°C, water at 38.5°C was added to the BOX. After 10 minutes the water in the BOX was chilled and maintained at 10.3°C for the remainder of the experiment. After a further 10 minutes, the WB was cooled at 0.6°C·min<sup>-1</sup> until all SkBF measures indicated vasoconstriction. SkBF responses were variable and mean plots misleading, those from subject 1 are in the figure. After approximately 5-15 minutes of cooling in the WB, profound vasoconstriction was usually indicated. In 5 of the 7 subjects vasoconstriction occurred simultaneously, as indicated by all 4 SkBF measurement techniques. In the other 2 subjects, at least one of the SkBF techniques indicated vasoconstriction before the other methods, or the responses were variable. Before cold-induced vasoconstriction occurred, each technique indicated variable SkBF responses, but in different subjects. For example, large reductions in SkBF (>20%) were indicated on filling the BOX with warm water in 2 to 4 subjects (hydrostatic effect), dependent upon the measurement technique. When the BOX was chilled, further reductions in SkBF (>20%) (thermal effect) were indicated in 2-4 subjects (generally the same subjects). For each SkBF technique, 3-5 subjects did not exhibit large changes in SkBF (>20%) when the BOX water temperature was cooled, but the WB remained high. These data suggest that any of the techniques may be used for detecting gross vasoconstrictive tone, but SkBF responses can vary significantly between techniques when vasodilated.

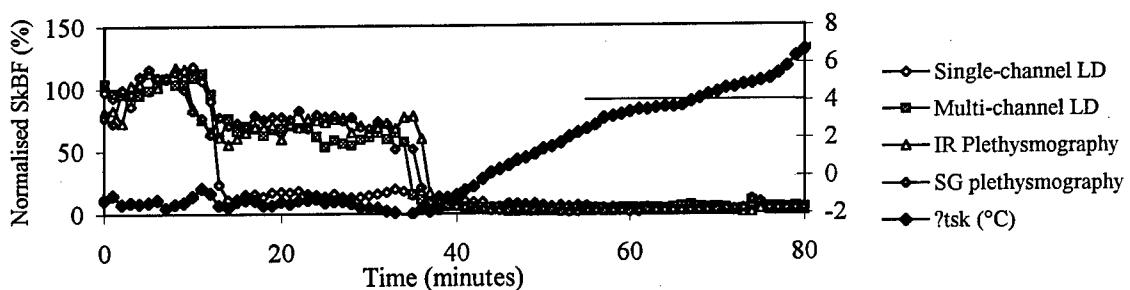


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## USING SKIN TEMPERATURE GRADIENTS TO ASSESS SKIN BLOOD FLOW

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The forearm-finger pad skin temperature differential ( $\Delta t_{sk}$ ) has previously been used as an estimation of cutaneous skin blood flow (SkBF), vasoconstriction being considered significant when  $\Delta t_{sk} \Delta 4^{\circ}\text{C}$  (Sessler *et al.*, 1988), on the basis that it "correlates well with other methods of determining cutaneous blood flow, including plethysmography". The original source data (Goetz, 1946) are from a study of SkBF (estimated by air-displacement plethysmography) and toe pad skin temperature only, not  $\Delta t_{sk}$ . Goetz (1946) concluded that skin temperature starts rising only after SkBF has been increasing for some time. Thus, the  $\Delta t_{sk}$  method would not seem to have been validated. This study was undertaken to assess if  $\Delta t_{sk}$  can predict vasomotor tone as indicated by 4 other methods of estimating SkBF (see: House & Tipton in these proceedings).  $\Delta t_{sk}$  was calculated from the difference between the radial mid-forearm skin temperature and that recorded from the index finger pad of the right hand. SkBF (4 techniques) was measured on the finger pads of the left hand which was immersed, without direct contact, in water at  $38.5^{\circ}\text{C}$  or  $10.3^{\circ}\text{C}$ , whilst the subjects were seated in a water bath heated initially to  $40.6^{\circ}\text{C}$  (see: House & Tipton in these proceedings for full methods). After ethical approval, seven medically fit volunteer subjects (6M 1F, aged 20-22 years) gave informed consent to participate. With heating, significant vasodilatation was indicated by all 4 methods, whilst  $\Delta t_{sk}$  was steady at  $-1.1^{\circ}\text{C}$  (SD 0.6). When the left hand had been cooled, and the bath was being cooled [ $-0.6^{\circ}\text{C} \cdot \text{min}^{-1}$  (SD  $0.2^{\circ}\text{C} \cdot \text{min}^{-1}$ )], the 4 SkBF techniques simultaneously indicated profound vasoconstriction in 5 of the 7 subjects. At the corresponding time  $\Delta t_{sk}$  started to increase approximately linearly. The response for subject 1 is shown in the figure. The point at which  $\Delta t_{sk}$  started to rise, termed the "inflection point" of the response, defines the time of vasoconstriction more accurately than a particular value of  $\Delta t_{sk}$ . For 4 subjects, the inflection point occurred simultaneously with vasoconstriction, as assessed by the other 4 methods. For the other 3 subjects, it occurred within 1 to 3 minutes. For 3 of the subjects,  $\Delta t_{sk}$  only reached a maximum of  $0.8^{\circ}\text{C}$  to  $2.7^{\circ}\text{C}$  and, by the original criterion, would not have been regarded as indicating vasoconstriction, despite its occurrence. For 4 subjects,  $\Delta t_{sk}$  reached  $4^{\circ}\text{C}$  25 to 31 minutes after vasoconstriction, as identified by the other SkBF techniques. It is concluded that the  $\Delta t_{sk}$  inflection point predicts cutaneous vasoconstriction better than  $\Delta t_{sk} \Delta 4^{\circ}\text{C}$ . The  $4^{\circ}\text{C}$  differential will confirm that vasoconstriction has occurred but not when, and not in all subjects.



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## THE CENTRAL PYROGENIC ACTION OF INTERLEUKIN-6 IS RELATED TO NUCLEAR TRANSLOCATION OF STAT3 IN THE ANTEROVENTRAL PREOPTIC AREA OF THE RAT

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Central administration of the cytokine and endogenous pyrogen interleukin-6 (IL-6) elicits a variety of (patho-)physiological functions, such as the reduction of food intake and locomotor activity, the activation of the hypothalamo-pituitary-adrenocortical axis and the mediation of fever responses. The effects of IL-6 and related cytokines are mediated via the GP130 receptor family. Stimulation of these receptors activate a cytokine-specific signal transduction pathway, the so-called Janus kinase-signal transducer and activator of transcription (Jak-STAT) signalling cascade. IL-6 is known to act through the STAT3-isoform which gets phosphorylated, dimerizes and then translocates into the nucleus, where it regulates gene expression by binding to specific gene promoters, amongst others the promoter of the immediate early gene c-fos. This conversion of a cytokine stimulus into a long-term genetic action and its exact neuroanatomical location was studied previously in rats combining systemic and central IL-6 treatment with FOS-immunohisto-chemistry or FOS *in-situ* hybridisation technique. When thereby assessing putative central IL-6 target structures a specific FOS-activation pattern was found within the vascular organ of the lamina terminalis (OVLT), its adjacent medial preoptic area (MPO) and also ependymal layers of the ventricles and meninges. In order to demonstrate the central pyrogenic action of IL-6, adult male Wistar rats were applied with a lateral ventricular cannula that was stereotactically inserted under general anaesthesia (100mg/kg ketamine and 10mg/kg xylazine). Then after a 10-12 days recovery period intracerebroventricular (icv) IL-6 bolus applications were performed with rat-recombinant IL-6 (100ng and 200ng in 5µl). Both IL-6 doses elicited a febrile response which was not observed in controls (5µl pyrogen free saline). The neuroanatomical basis of central IL-6 receptor activation on STAT3-proteins was investigated via central IL-6 stimulation combined with immunohistochemical procedures. Rats were perfused 15-90min after the icv stimulation, the brains were removed and analysed for STAT3-immunoreactivity which was additionally co-localised with the nuclear DAPI stain. In saline-treated animals constitutive STAT3-expression was low at all time points and predominantly detected within the cytoplasm of large cells within ventral aspects of the medio-caudal hypothalamus. In IL-6-treated rats an intense STAT3-expression and -translocation into cell nuclei was observed at 15-30min after icv treatment in various fore- and hindbrain sites. In particular, IL-6 induced a pronounced nuclear STAT3-translocation in the rostral hypothalamus, e.g. in the MPO and its ventromedial part and also in the lateral OVLT. The observed nuclear staining pattern was similar to that seen with FOS-analysis after IL-6 or endotoxin (LPS) treatment. The size and shape of the stained nuclei suggest that STAT3-immunoreactivity was predominantly located in neurons, but IL-6 also induced a prominent nuclear labelling in ependymal, meningeal and glial cells. Nuclear translocation of immunoreactive STAT3 therefore represents a novel and powerful tool to assess central IL-6 actions upstream of IL-6-induced c-fos gene activation. The results further support the importance of the OVLT and its adjacent preoptic area as main central IL-6 targets involved in the mediation of fever responses.

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## CENTRAL EFFERENT PATHWAYS CONTROLLING EVAPORATIVE HEAT LOSS IN THE RAT

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Rats exposed to extreme heat stress (40°C) neither sweat nor pant. Instead they activate other heat loss mechanisms such as skin vasodilation, especially of the tail, and they also salivate and spread the saliva on their skin and fur to remove heat by evaporation. For saliva-spreading, the submandibular and the sublingual glands are primary thermoregulatory effector organs under such conditions. Saliva lost under heat stress has severe implications for the rats' body fluid economy and contributes to thermal dehydration and subsequent thirst. The importance of the rostral hypothalamus in particular the anteroventral wall of the third ventricle (lamina terminalis) in the control of body fluid homeostasis has been clearly demonstrated. Far less data are available concerning a possible role of the lamina terminalis in the control of body temperature. However, lesioning studies in the rat, that included the lamina terminalis and parts of the preoptic area or the anterior hypothalamus, led to severe deficits in regulating body temperature under heat stress and clearly affected the thermoregulatory secretory function of salivary glands. In order to neuroanatomically demonstrate central efferent pathways controlling heat-induced salivation, including those arising from the rostral hypothalamus, we employed the viral tracing technique, that uses the transsynaptic retrograde transport of an attenuated strain of pseudorabies virus (PRV-Bartha) for neuronal tract tracing. In an attempt to further distinguish the central efferent outflow towards the salivary gland innervation, viral inoculations were combined with ipsilateral chorda tympani destruction (parasympathectomy), removal of the ipsilateral superior cervical ganglion (sympathectomy) and total ipsilateral efferent denervation (parasympathectomy and sympathectomy). In addition, the immunohistochemical detection of the neuronal activation marker c-Fos was used as a more functional approach to neuroanatomically demonstrate central structures activated in the heat (2h, 40°C). Unilateral injections of PRV-Bartha into as well as surgical denervation of the left submandibular or sublingual gland were performed in male Sprague-Dawley rats (250-350 g) under general anaesthesia with sodium pentobarbitone (60 mg/kg, i.p.). For the histological brain analysis rats were (re-)anaesthetized (100 mg/kg pentobarbitone, i.p.) after a 1-4 day tracing period or after 2 h heat stress, respectively, and then transcardially perfused with 0.9% saline followed by 4% paraformaldehyde/phosphate buffer. Inoculation of the glands revealed multisynaptic neuronal pathways arising from various forebrain regions including the entire lamina terminalis. The denervation experiments suggested that the first wave of lamina terminalis infection was due to efferent connections directed towards the parasympathetic submandibular gland innervation. Heat stress induced a clear Fos-activation in many brain structures when compared to the controls and again the lamina terminalis and in particular its median preoptic nucleus showed an intense Fos-response. These data suggest that one efferent forebrain pathway influencing salivary secretion under heat stress may originate in the lamina terminalis and may be used especially under heat stress-induced hyperthermic and hyperosmolal conditions. Therefore a key to the understanding of the central regulation of heat induced salivation in the rat may be the unravelling of the integrative role of the lamina terminalis in processing thermoregulatory and osmoregulatory information.

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## CONSIDERING INDIVIDUAL PHYSIOLOGICAL DIFFERENCES IN A HUMAN THERMAL MODEL

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Over the last few years, UCB has developed a comprehensive model of human thermoregulation and comfort. This model is based on the Stolwijk model of human thermal regulation but includes several significant improvements including the ability to model an unlimited number of body segments (compared to six in the original) and a counter-current heat exchange blood flow model. Radiation heat transfer is calculated by the view factor method using a three-dimensional model of the body. It is thus possible to do a detailed assessment of complex radiative environments including the effects of solar radiation. The model is capable of predicting physiological response to transient, non-uniform thermal environments, and closely reproduces the results of many experiments in the literature.

Physiological differences between individuals can significantly affect human thermal response to the environment yet models of human thermal regulation have generally not taken this into account. Most thermal models use a single set of physiological data to represent an average person. We have developed a model that we call "body builder" that translates descriptive data about an individual (height, weight, body fat, gender, skin color and body type) into a set of physiological parameters that can be used by thermal models. Through literature review, we have selected what we feel are the best descriptive equations to calculate physiological parameters such as body fat, body density, basal metabolic heat production, blood flow rates, body segment length, and solar absorption. We have incorporated this "body builder" model into our thermoregulatory model and can use it to predict variations in thermal response between individuals. This paper presents the "body builder" model as well as preliminary comparisons between thermal simulation results and experimental data found in the literature.

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## ROLE OF THE PO/AH AND MRN ON THERMOREGULATORY SYSTEM IN FREELY MOVING RATS

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It is well established that the preoptic area and anterior hypothalamus (PO/AH) is the center of both heat production and heat loss responses. However, an alternative theory of thermoregulation was suggested by the finding that heat production responses were maintained when the PO/AH was destroyed. Furthermore, electrical stimulation of the ventromedial (VMH) and posterior (PH) hypothalamus increased non-shivering and shivering thermogenesis, respectively. Together, the PO/AH may not be involved in heat production. Several mechanisms are thought to be involved in heat regulation. In this regard, there is sufficient evidence to indicate that serotonin (5-HT) is a major neurotransmitter that mediates heat regulation in the hypothalamus. The hypothalamic serotonergic fibers are derived from cell bodies in the raphe nucleus, particularly the median raphe nucleus (MRN). However, the relationship between 5-HT and body temperature (Tb) remains unclear. The purpose of this study was to clarify the role of the PO/AH in thermoregulation and to examine the effects of serotonergic innervation from the MRN on Tb. We perfused tetrodotoxin (TTX) solution into the PO/AH and MRN using a microdialysis technique at three different ambient temperatures (5, 23, 35°C) in freely moving rats.

Male Wistar rats (250-350 g body weight) were housed separately in plastic cages under controlled conditions of ambient temperature 23°C, relative humidity 50% and a light-dark cycle of 12:12 h (lights on at 0600 h) with free access to food and water. A telemetry device and microdialysis probe were implanted surgically prior to the commencement of the experiments (Yasumatsu *et al.*, 1998; Hasegawa *et al.*, 2000). General anesthesia was induced with Nembutal (50 mg/kg, i.p.), the telemetry device was implanted in the peritoneal cavity, and the tip of a microdialysis probe was stereotactically placed in the left lateral PO/AH and in the left lateral MRN. Ambient temperatures were set at 23°C (normal environment), and 35°C (heat exposure) or 5°C (cold exposure) for 3 h to elicit changes in thermal balance in rats. In the normal environment, TTX solution (5 µM) was perfused for 1 h in the PO/AH and MRN. In the heat and cold exposure experiments, TTX was perfused during the last one hour of each exposure. At the end of each experiment, the locus of the microdialysis site was verified on histological sections.

In the MRN, perfusion of TTX solution induced significant hypothermia in the normal environment, a greater decrease in Tb during cold exposure and had no effect on Tb during heat exposure. In the PO/AH, perfusion of TTX solution induced significant hyperthermia in normal environment, a greater increase in Tb during heat exposure and had no effect on Tb during cold exposure. Our results indicate that the PO/AH regulates heat loss but not heat production. Heat production appears to be regulated by other areas receiving serotonergic innervation from the MRN.

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## THE EFFECTS OF THE TWO PHASES OF THE MENSTRUAL CYCLE ON TEMPERATURE RESPONSES TO EXERCISE IN THE HEAT IN HUMANS

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Eumenorrheic women have a biphasic rhythm in basal body temperature (BBT) during the menstrual cycle (MC). BBT is up to 0.5 °C higher during the luteal phase, which is accompanied by an increase in core temperature threshold for sweating and cutaneous vasodilation. BBT remains elevated for approximately two weeks until it decreases again at the onset of menstruation. This study investigated whether the alteration in thermoregulatory set point during the MC affects the temperature response to exercise in the heat. Eleven recreationally active women volunteered to randomly undertake two exercise tests during one MC. One test was conducted during the follicular phase (day 3-6) and one test during the luteal phase (day 20-24). For each subject both tests were conducted at the same time of day. The subjects exercised for 45 minutes on a cycle ergometer at 60% of their  $VO_{2\text{peak}}$  in hot, humid conditions (32 °C, 60% relative humidity). Rectal temperature ( $T_{re}$ ) and skin temperature ( $T_{sk}$ ) were measured. Mean  $T_{sk}$  was calculated according to Ramanathan (1964). Repeated measures ANOVA was used to compare  $T_{re}$  and mean  $T_{sk}$  between the two phases of the MC at 15 minute intervals. The average (SE) age, height and weight of the subjects was 24 (1.2) years, 167 (1.2) cm and 68 (3.1) kg respectively. No significant differences in mean  $T_{sk}$  were found between the MC phases at any time point.  $T_{re}$  did show a significant difference between the MC phases over time. Post hoc within subject contrasts showed a significant difference ( $p = 0.05$ ) between MC phases at 45 minutes of exercise. The Table shows the mean  $T_{re}$  (SE) in °C for both phases of the MC at the 4 time points.

$T_{re}$ in °C	Start	15 minutes	30 minutes	45 minutes
Follicular phase	37.01 (0.10)	37.34 (0.08)	37.76 (0.10)	38.12 (0.13)
Luteal phase	37.01 (0.11)	37.41 (0.09)	37.87 (0.08)	38.27 (0.11)

The mean  $T_{re}$  at the start of exercise was identical for both phases. This contradicts the expectations for an ovulatory MC and might indicate that some of the subjects did not ovulate during the testing cycle. Although the small difference in  $T_{re}$  between phases could also easily be masked by slight changes in pre test activity. The Table shows that  $T_{re}$  during the luteal phase increases at a slightly higher rate than during the follicular phase, which is confirmed by the significant higher  $T_{re}$  at 45 minutes during the luteal phase. This difference in the rate of increase between the two MC phases might be explained by the higher thermoregulatory set point during the luteal phase. The subjects started exercise at the same  $T_{re}$ , but since the threshold for sweating and vasodilation are higher during the luteal phase these effects would have started at a later time point during the test than during the follicular phase. Therefore for the present study  $T_{re}$  would have increased at a higher rate during the luteal phase than during the follicular phase.

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## **SITES AND CELLULAR MECHANISMS OF HUMAN ADRENERGIC THERMOGENESIS – A PROPONENT'S VIEW**

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Evidence in the literature clearly documents existence of nonshivering thermogenesis of adrenergic origin in adult humans. This thermogenesis is activated in cold exposed individuals, during the early phase of cooling, prior to the start of shivering and equals to about 25 % of the basal metabolic rate ( $0,29 \text{ W kg}^{-1}$ ). This amount of heat can compensate for heat loss from the body when the air temperature is about  $5^\circ \text{ C}$  below the thermoneutral zone. Human nonshivering thermogenesis is probably based on thermogenic actions both of adrenaline and noradrenaline. Relative participation of adrenaline or noradrenaline in the thermogenic response is not known, however, and the mode of action of both amines may be different. In contrast to noradrenaline thermogenesis, the adrenaline thermogenesis can to be potentiated by cold adaptation to the level corresponding to the total capacity of beta adrenergic (isoprenaline) thermogenesis ( $0,53 \text{ W.kg}^{-1}$ ). Adrenaline thermogenesis is located in skeletal muscles and probably also in the white fat. Diffused brown fat cells appearing inside of white fat pads may be also involved. Although several molecular mechanisms have been suggested, the discrete mode of catecholamine thermogenic action in organs other than the brown adipose tissue remains unknown. It was found that the adrenergic thermogenesis is mediated by  $\beta 1$  and  $\beta 2$  adrenoceptors, however. Possible involvement of  $\beta 3$  adrenoceptors and of uncoupling proteins UCP 2 and UCP 3 is to be also considered, although the direct evidence for their involvement in human adrenergic thermogenesis is still missing. Regulatory mechanisms based on changes in blood flow also may play a role.

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## DIFFERENT PYROGENS INDUCE DIFFERENT CHANGES IN THE IMMUNE RESPONSE

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In order to specify the role of individual cytokines in the immune response under in vitro conditions, isolated and cultivated human peripheral blood mononuclear cells (PBMC) were used for experiments. Different pyrogens (lipopolysaccharide from Esch. coli - LPS, live Borrelia burg.) were applied and the time course of changes in concentrations of different cytokines in the medium were measured using the ELISA method. It was found that activation of PBMC by LPS increases production of IL 1 $\beta$ , TNF $\alpha$  and IL 6 significantly. Production of IL 10, IL 12 and INF $\gamma$  gama was not influenced. In contrast to LPS, infection of PBMC by live Borrelia, besides IL 1 $\beta$ , TNF $\alpha$  and IL 6, also increases production of IL 12 and IFN $\gamma$ . Production of IL 1 $\beta$ , IL 6 and TNF $\alpha$  increases immediately after incubation both with LPS and Borrelia, while production of IL 12 and INF gama starts to increase only after 8 hour of cultivation. Data suggest that activation of the immune cascade due to infection of different pyrogens is being realized by different membrane receptors and by different transmission pathways. Infection by Borrelia activates not only the early steps of the immune response (macrophages and T cells), but also the late phase of the immune cascade, probably due to activation of killer cells. Results indicate that under in vivo conditions the febrile state could be induced and maintained due to action of different cytokines.

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## VASOMOTOR CHANGES IN HUMANS INDUCED BY LOCAL PERIPHERAL COOLING

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The aim of the study was to find out to which extent the local peripheral cooling can induce physiological responses similar to those observed after whole body cooling (Janský et al., 1996). It was found that immersion of legs (up to the knees) into the cold water (13° C) induces immediate decrease in toe and calf skin temperatures down to the level of water temperature. This response is completed within 5 min and persists for the whole period of cooling (40 min), indicating strong vasoconstriction in the immersed parts of the body. No signs of cold induced vasodilation (CIVD) were observed. Skin temperatures in the nonimmersed parts of the body do not change significantly. There is a trend for a small decrease of skin temperature on the chest and a trend for an increase in skin temperature on fingers, however. Rectal temperature, metabolic rate, heart rate and blood pressure do not change during cold water immersion of legs. Only nonsignificant changes in noradrenaline and adrenaline concentrations in the venous blood were found, indicating very small or transitive involvement of the sympathetic nervous system. Repeated cold water immersions of legs (30 min, 5 times a week for a period of 3 weeks) increase skin temperature of nonimmersed parts of the body (chest, fingers), thus indicating attenuation of vasoconstriction and greater supply of the warm blood to the skin. Since no significant changes in sympathetic activity occur, the role of downregulation of adrenergic receptors or of humoral vasodilatators should be taken into consideration. Physiological significance of this adaptational phenomenon is not clear. Rectal temperature also tends to increase after repeated immersions of legs, which contrasts with our earlier observations obtained on humans exposed to repeated head-out cold water immersions (Janský et al., 1996). Metabolic, insulative and hypothermic types of adaptation, which typically occur in cold adapted humans, were not observed after repeated cold water immersions of legs. Neither the CIVD, occurring in hands immersed into the cold water, was influenced by repeated cold water immersions of legs.

Janský et al., (1996) *Pflügers Archiv European Journal of Physiology*, 432, 368-372.

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## PHARMACOLOGICAL BLOCKADE OF NEURAL TRANSMISSION: LESSONS FROM EXPERIMENTS INVESTIGATING CUTANEOUS BLOOD FLOW

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The spatial discrimination in the measurement of blood flow offered by laser-Doppler flowmetry, when coupled with the local application of specific agonists or antagonists, has led to new insights in our understanding of the mechanisms of control, both neural and local, of the cutaneous circulation in humans. The reflex control of that circulation involves both adrenergic vasoconstrictor nerves and a non-adrenergic active vasodilator system. The application of bretylium to a small area of skin by iontophoresis blocks transmitter release from adrenergic nerves in that area and allows unambiguous observation of vasodilator function. Through this approach it was discovered that both thermoregulatory reflexes and non-thermoregulatory reflexes (baroreflexes, exercise), control both the vasoconstrictor and the active vasodilator systems. Post synaptic blockade of both alpha and beta adrenergic receptors through intradermal injections of yohimbine and propranolol was effective in completely inhibiting the vasomotor responses to exogenous norepinephrine, but was only partially effective in inhibiting reflex vasoconstrictor responses to body cooling. This finding is highly suggestive of significant cotransmitter function in adrenergic vasoconstrictor nerves. Post-synaptic beta-adrenergic blockade through application of propranolol alone and testing with isoproterenol by intradermal microdialysis revealed the presence of beta-adrenergic receptors in the skin. The vasoconstrictor responses to local skin cooling were reversed by the local iontophoretic application of bretylium, indicating that the response is dependent on a functional vasoconstrictor system. The use of iontophoretically applied atropine eliminated the vasodilator response to exogenously applied acetylcholine, but was only partially effective in inhibiting the reflex vasodilator response to body heating. Reflex active vasodilation was completely inhibited by the intradermal injection of the presynaptic cholinergic nerve antagonist botulinum toxin. Taken together, these findings strongly indicate an important role for a cotransmitter released from cholinergic nerves as part of the mechanism for active vasodilation. Preliminary findings through the application of antagonists through intradermal microdialysis suggest VIP as a good candidate for the cotransmitter. Finally, the use of nitric oxide synthase inhibitors applied via intradermal microdialysis showed a partial inhibition of active reflex vasodilation and an almost complete inhibition of the vasodilator response to local warming, showing roles for nitric oxide in both local and reflex effects of heat on the skin.

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## CHANGE IN LOCAL EVAPORATION RATES IN RESPONSE TO TEMPERATURE INCREASES TO 33, 36 AND 39°C FROM 28°C

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A new device to measure local evaporation rates more precisely has been developed by the author (Kakitsuba & Katsuura, 1992), by improving the gradient method first proposed by Lamke (1977). Using this device, temperature and relative humidity at three different points within a boundary layer on the skin can be measured to predict a real distribution of absolute humidity on the skin. In the present study, four young male subjects were exposed to 33, 36 and 39°C for 40 min, following a 20-min control exposure at 28°C. Subjects were clothed only in swimming trunks, and sat on a reclining chair throughout exposure. Local evaporation rates, skin temperatures, heat flow rates at forehead, chest, upper arm, thigh and calf were continuously measured. Oesophageal temperature, ECG and metabolic rate were also continuously measured. In addition, thermal and comfort sensation votes were recorded at 5-min intervals. Evaporation rates ( $m_{sk}$ ) at all sites gradually increased, but did not reach a plateau at 33°C. However,  $m_{sk}$  increased promptly during the first half of exposure, and reached a plateau at 36 and 39°C. Knowing that  $m_{sk}$  remains unchanged, or slightly decreases, when the skin is fully wetted with sweat, the critical  $m_{sk}$  value (the maximum evaporative capacity for a given thermal condition) can be identified. Local evaporative heat transfer coefficients ( $he$ ) at three sites were then calculated:

Sites	$he$ (W/m <sup>2</sup> /mmHg)
Forehead	6.8
Front thigh	6.2
Chest	5.7

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## CIRCADIAN VARIATIONS IN THE ROLE OF NITRIC OXIDE IN THERMOREGULATION, FEEDING AND ACTIVITY IN UNRESTRAINED RATS

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The role of nitric oxide in thermoregulation, feeding behaviour and activity has been studied only during the day and mainly in nocturnally-active animals. Such animals have low daytime food intake, body temperatures and activity levels, which may confound any effects manipulation of nitric oxide may have. Thus, we have investigated whether the effects of decreased nitric oxide synthesis on these three variables is influenced by circadian rhythm in a nocturnal animal, the rat. Individually-caged female Sprague-Dawley rats (200-250 g), housed at ~24°C with a 12:12 h light:dark cycle (lights on 07:00-19:00) and provided with food and water *ad libitum*, were used. We inhibited nitric oxide synthesis by administrating N-nitro-L-arginine methyl ester (L-NAME), a non-specific inhibitor of all nitric oxide synthase isoforms, and aminoguanidine, a relatively selective inhibitor of the inducible isoform of nitric oxide synthase. Four doses of L-NAME (100, 50, 25 and 10 mg/kg) and two doses of aminoguanidine (100, 50 mg/kg) were used. Rats were divided into six groups of six animals each; animals in each group served as their own controls, receiving, in random order, intraperitoneal injections of one of the drug doses or saline during the day (~09:00) or night (~21:00), with seven days between each injection. Body temperature and activity were measured using radiotelemetry; the telemeters were implanted under ketamine: xylazine anaesthesia at least one week before the start of experimentation. Food intake was calculated by weighing each animal's food before and 12 and 24 hours after each injection. Injection of all doses of L-NAME at 09:00 had no significant effect on daytime body temperature, food intake or activity. However, daytime injection of L-NAME decreased nighttime activity (all doses,  $P < 0.05$ ) and food intake (25, 50 and 100 mg/kg,  $P < 0.05$ ), but did not affect nighttime body temperature of the rats. Similarly, injection at 09:00 of either dose of aminoguanidine did not affect daytime body temperature, food intake or activity levels, but decreased nighttime feeding and activity (both doses,  $P < 0.05$ ) whilst not affecting nighttime body temperature. Injection of L-NAME at 21:00 caused eight to ten hours of hypothermia of ~ 0.6°C, which started one to two hours after injection (50 and 100 mg/kg,  $P < 0.05$ ), reduced that night's activity (25, 50 and 100 mg/kg,  $P < 0.05$ ), and caused a dose-dependent drop in food intake at all doses ( $P < 0.05$ ). On the other hand, injection of aminoguanidine at 21:00 did not cause hypothermia or affect nighttime food consumption, but did reduce that night's activity when the 100 mg/kg dose was injected ( $P < 0.05$ ). The effects of nitric oxide synthase inhibition on body temperature, feeding and activity are therefore influenced by circadian rhythm. Also, inducible nitric oxide synthase may be involved in the regulation of feeding and activity but does not appear to play a role in normal thermoregulation in rats.

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## ESTIMATION OF METABOLIC RATE FROM CARDIAC FREQUENCY FOR FIELD STUDIES: CORRECTING FOR "THERMAL PULSES"

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With increasing mechanization of production usually metabolic rate will not constitute a limiting factor by itself, but is needed to assess thermal strain especially in hot working conditions. The oxygen consumption can be measured directly (e.g. by a respiratory gas clock); the measurement cannot be made continuously throughout a complete shift and usually is restricted to time intervals below 20 minutes. Several authors have linked metabolism to cardiac frequency because cardiac frequency can be measured during complete shifts. However, the metabolism estimated from cardiac frequencies in the field usually was higher than the directly measured metabolism; this overestimation is caused by the different influences of static work components, stress, dehydration etc. on cardiac frequencies in the field. In case of hard physical work or climatic load cardiac frequency may increase considerably with elevated body temperature. Vogt *et al.* (1970) proposed a methodology to assess the fraction of cardiac frequency that is caused by elevated body temperature ("thermal pulses"): as the time constant of the cardiovascular system is much shorter than the time constant for heat loss of the body, they proposed to use the cardiac frequency in the fourth minute after the begin of a resting break to estimate the cardiac frequency that is caused by the elevated body temperature itself. If there is a sufficient number of breaks during a shift, the cardiac frequency may be corrected for the thermal pulses by linear interpolation between these breaks but this correction is not adequate for the time in between, especially if high work load is present between these breaks. For a study concerning the strain of miners at hot working places we developed a procedure improving Vogt's method by using continuous measurements of body temperature: by plotting the values of cardiac frequency over the values of body temperature for each shift we got diagrams showing the lowest cardiac frequency occurring for each value of body temperature: by smoothing this characteristic we get a gauge function to correct the cardiac frequencies for thermal pulses throughout the shift for all levels of body temperature. This correction was applied for a field study of physiological strain of coal miners at hot working places (38 miners in a total of 112 shifts). As a result, the cardiac frequencies at the working site that increased for  $36 \text{ min}^{-1}$  above the resting values (mean values for all shifts) showed a fraction of thermal pulses amounting to  $12 \text{ min}^{-1}$ . For the complete shifts (descent – ascent) the increase of cardiac frequencies above resting values was  $30 \text{ min}^{-1}$ ,  $9.4 \text{ min}^{-1}$  of which could be classified as thermal pulses. – Correspondingly, the increase of metabolic rates due to the work (mean  $\pm$  std.dev.) reduced from  $(305 \pm 108) \text{ W}$  to  $(223 \pm 77) \text{ W}$  during the time at the working site, when estimated from a set of simultaneous measurements of oxygen consumption and cardiac frequency in underground work. This methodology allows to evaluate the fraction of cardiac frequency that is caused by the increase of body temperature throughout complete shifts, if body temperature is measured continuously and if enough breaks have been made during a shift. In mechanized coal mining, the last condition usually is fulfilled due to the sequence of operations.

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## THE ROLE OF CENTRAL THERMAL SIGNALS IN MODULATING THERMOEFFECTOR FUNCTIONS

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The body temperature of homeothermic animals is regulated by systems that utilize multiple behavioral and autonomic effector responses. The thermoreceptors that provide inputs to the regulatory systems are distributed throughout the body. Although the regulatory aspects of this multiple-input/output system are largely nervous, knowledge about the "neuronal circuit" for thermoregulation remained rather stagnant for several decades. However, the last few years have brought new approaches that have led to new information and new ideas about neuronal interconnections in the thermoregulatory network (Kanosue et al., 2000). This is especially true for efferent pathways from the preoptic area. Recent studies utilizing chemical stimulation of the preoptic area revealed that not only heat loss but also heat production responses are controlled by warm-sensitive neurons in the preoptic area. These neurons send excitatory efferent signals for the heat loss and inhibitory efferent signals for the heat production. The warm-sensitive neurons that control these two opposing responses are different and work independently. Recent analysis revealed many crucial sites along efferent pathways from the preoptic area to various thermoregulatory effector organs. The efferent systems for skin vasomotion and nonshivering thermogenesis have been especially studied in detail. As for skin vasomotion, vasoconstrictive and vasodilative neurons were found in the ventral tegmental area and the rostral part of the periaqueductal grey (PAG), respectively (Zhang et al., 1997). Both of them receive inputs from the preoptic area. In the medulla oblongata premotor neurons are located in the raphe nucleus (Rathner and McAllen, 1999), which send axons to the spinal cord. As for nonshivering thermogenesis, tonically inhibitory mechanism was identified in the area including the nuclei of the retrorubral field (Shibata et al., 1999). And we have recently found the neurons in the caudal part of the PAG sending excitatory signals to the brown adipose tissue. In the medulla oblongata, the raphe nucleus (Morrison, 1999) and the inferior olive (Uno & Shibata, 2000) have been suggested as the crucial sites for the control of nonshivering thermogenesis. Even though many neurons and connections in the efferent pathways remain unidentified, recent advances in experimental techniques promise a much more detailed understanding of the neuronal circuit underlying thermoregulation in the near future.

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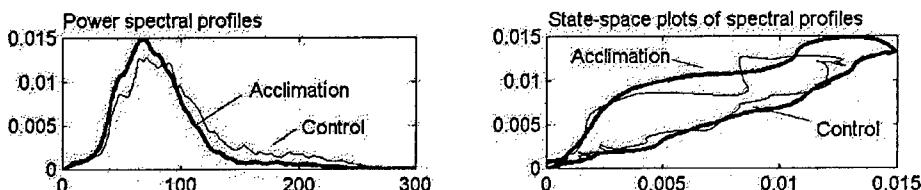
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## ASSESSMENT OF HEAT-ACCLIMATION STATE IN RATS THROUGH THE SPECTRAL ANALYSIS OF THE EKG SIGNAL

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The heart rate variability (HRV) has been widely used to assess the cardiac condition as well as the physiological state of humans and animals. In these studies, usually the HRV series or the R-R interval (RRI) series derived from the EKG signal are analyzed using spectral decomposition methods. In the present work, EKG signal has been analyzed to assess the state of heat acclimation in rats. *Materials and methods:* Adult, male Sprague-Dawley rats were divided into control (C) and heat acclimation (HA) groups (male, N=6 per group). Telemetry transmitters were surgically implanted into rats (sodium pentobarbital 50 mg/kg, i.p., supplemented, as required, with methoxyflurane to maintain anesthesia) 2 weeks prior to starting data collection. Initially, both the groups were housed at 26°C, 50% rh. HA, unrestrained rats were subsequently housed at 32-33°C, for 2 weeks. ECG signals (sampled at 1000Hz, 10 sec strips every 10 min for 1 hour) were collected at the same time of day 3 days a week prior to and throughout the 2 weeks of acclimation. Power spectral density of unit time-differenced EKG series were computed using Welsch's method. To compute the average energy pattern for the HA rats, singular value decomposition (SVD) was used (see: Kanjilal, 1995). The individual profiles were arranged into the rows of a matrix, which was SV-decomposed; the average energy pattern was estimated from the first column of the right singular vector matrix. *Results:* Spectral profiles for the rats showed significantly smoother profiles following HA compared to the same for the C rats. The average energy pattern for the HA population (computed from the EKG obtained on the sixth recorded day) and the same for a C rat over six days are shown in the Figure. The HA and the C states are conspicuously different in the state-space plot for the estimated spectral pattern series  $\{x(k)\}$  against  $x\{k+9\}$ . The state-space plots of the spectral profiles for the individual rats are observed to be a direct means of qualitative assessment of the HA state of the animals. The comparative analysis using Mann-Whitney rank sum statistic (MWRS) between profiles for the successive days shows that subsequent to acclimation, the MWRS usually drops to  $<1$ , whereas it remains  $>1$  and usually  $>1.96$  for the C group. Our findings provide evidence that sympathetic drive, during the heat acclimated state, becomes reduced possibly affecting cardiac contractility. These findings have important clinical implications in controlling cardiovascular risk factors.



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## **DECREASED ACTIVE CUTANEOUS VASODILATATION IN AGED SKIN: MECHANISMS, CONSEQUENCES, AND INTERVENTIONS**

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Despite early reports to the contrary, it is now well recognized that aged men and women respond to heat stress with an attenuated increase in skin blood flow (SkBF). While other human thermoregulatory adjustments and responses to hyperthermia are highly dependent on other factors -- aerobic capacity (VO<sub>2</sub>max), acclimation status, hydration, diseases and medications -- the relative inability of aged skin to vasodilate appears to be a primary consequence of advanced age. For example, while a healthy acclimated 65-year old athlete will respond to exercise in a hot environment with a similar increase in body core temperature and sweating rate as a VO<sub>2</sub>max-matched 30-year old, SkBF may be 30-50% lower. Over the past 10 years we have examined the neural and cardiovascular mechanisms underlying and supporting this age-related decrement, the potential health-related consequences of the integrated cardiovascular response of older individuals exposed to heat stress, and interventions which have been shown to increase cutaneous vasodilatation in the elderly. Elimination of sympathetic cutaneous vasoconstriction via either alpha-adrenergic receptor blockade or by preventing local release of norepinephrine does not selectively increase SkBF in heat-stressed older human subjects. Rather, structural changes in aged skin coupled with a decreased active vasodilator sensitivity account for the altered control of SkBF. The potential role of nitric oxide-mediated mechanisms is currently under investigation. On the supply side, the lower SkBF response of the elderly is accompanied by both a smaller increase in cardiac output and a lesser redistribution of flow from splanchnic and renal circulations. The relative inability to maintain stroke volume in light of a falling central venous pressure and attenuated increase in cardiac output may be secondary to the decreased beta-adrenergic sensitivity which accompanies aging. In the healthy older population, aerobic conditioning, heat acclimation, and, in the case of postmenopausal women, unopposed exogenous estrogen have all been shown to increase SkBF at a given core temperature. While the primary purpose of increasing human SkBF in hyperthermic conditions is to transfer and dissipate heat, the principle challenge of aged individuals exposed to heat stress is not to thermal homeostasis, but rather to cardiovascular homeostasis.

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## ENDOTHELIAL NITRIC OXIDE SYNTHASE (e-NOS) IS HIGHLY EXPRESSED IN BROWN ADIPOSE TISSUE

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Brown adipose tissue (BAT) is the unique organ that specializes in heat production in the body and is the major site of nonshivering thermogenesis during cold acclimation. Blood flow through BAT is directly related to its thermogenic state and high rate of blood flow is required for heat production in BAT to provide oxygen and to transfer heat. Noradrenaline released from sympathetic nerve terminals in BAT is involved in the regulation of BAT blood flow, however, the mechanism of vasodilatation by noradrenaline in BAT has not been well elucidated. Concerning this regulatory mechanism, we have previously shown that noradrenaline may induce a production of nitric oxide (NO) in BAT, resulting in an increase in its blood flow. NO is produced by NO synthase (NOS), constitutive and inducible isoforms, both of which have been identified. However, it has not been determined which NOS isoform is involved in the control of BAT blood flow. Since noradrenaline increases BAT blood flow within a minute, it is likely that constitutive NOS-produced NO regulates the blood flow through BAT. To ascertain this possibility, we studied the expression of two constitutive NOS (e-, b-NOS) in BAT. Further, we examined the effect of cold exposure for 24 hours on the expression of these genes. Male Wistar rats were killed by decapitation and interscapular BAT was excised quickly, and then total RNA and protein were prepared. Reverse transcriptase-polymerase chain reaction (RT-PCR), Northern and Western blot analyses were performed to identify the isoforms of constitutive NOS. In control rats, e-NOS mRNA was highly detected, while b-NOS mRNA was not in BAT. The high level of e-NOS mRNA was also detected in isolated brown adipocytes. Similar results for protein level of NOS were obtained by Western blot analysis. Cold exposure led to an increase in e-NOS mRNA expression. Intraperitoneal injection of beta3-adrenoceptor agonist, which is responsible for BAT thermogenesis, also elevated the level of e-NOS gene expression. These results suggest that NO produced by e-NOS in BAT may regulate BAT blood flow, and activity as well as expression of e-NOS are controlled by an activation of sympathetic nervous system. Furthermore, NO derived from brown adipocytes may be involved directly in metabolic activity of this tissue, since we have previously reported that the administration of NOS inhibitor depressed the in vitro oxygen consumption of BAT. Thus, NO might be one of the essential regulators involving in BAT thermogenesis. However, neither localization site for e-NOS nor signaling pathway for activating e-NOS in BAT has been clarified. To understand the physiological role of NO in BAT, further studies are warranted to elucidate these points.

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## FOS EXPRESSION INDUCED BY LOCAL WARMING OR COOLING OF THE PREOPTIC AREA IN RATS

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The preoptic area plays an important role as a thermosensitive site for body temperature regulation: local warming or cooling there produces variety of thermoregulatory effector responses. To elucidate the functional projection from the preoptic area, we analyzed Fos expression during thermal stimulation of the preoptic area. Male specific pathogen-free crj-Wistar rat (300-350 g; Charles River Japan, Osaka Japan) was anesthetized with sodium pentobarbital (1 ml/kg, i.p.). A water-perfused thermode was chronically implanted into the brain so that its tip was positioned just rostral to the preoptic area (0.0 mm to bregma, 1.0 mm from midline and 8.8 mm below the skullface). Brain temperature was measured with a thin thermocouple glued to the thermode tip and body temperature with a thermocouple implanted in the peritoneal cavity. Throughout the recovery and experimental periods the rat was put in a box (30 cm in diameter, 30 cm height), the floor of which rotated the same angle in the opposite direction to the rat's rotation, so that thermode tubes and lead wires were not twisted. In this box, a rat can move freely during brain thermal stimulation. During 140 min experiment room temperature was set at 26 °C. The brain temperature was maintained at 37.5 °C except the period from 60th to 90th min, when the brain was warmed to 42 °C or cooled to 33 °C. As soon as the brain warming or cooling started, body temperature decreased or increased, respectively. This indicates that the thermode was appropriately located at thermosensitive region in the preoptic area. At the 140th min rats were deeply anesthetized with sodium pentobarbital (2.5 ml/kg, i.p.) and perfused transcardially. Fos expression of the rat brain was analyzed with immunohistochemical method. The local warming of the preoptic area induced intensive elevation of Fos immunoreactivity around the thermode. On the contrary, the local cooling of the preoptic area did not produce any specific Fos expression in the preoptic area itself. These results suggest that the number of cold-sensitive neuron in the preoptic area is far smaller than warm-sensitive neurons. Outside the preoptic area, the local warming of the preoptic area produced intense elevation of Fos immunoreactivity in the supraoptic nucleus and the rostral part of the periaqueductal grey matter. The local cooling of the preoptic area produced Fos immunoreactivity in the anterior hypothalamus and the caudal part of the periaqueductal grey matter. These areas would receive information concerning local brain temperature of the preoptic area, and involve in some ways in thermoregulation.

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## THE MECHANISMS OF FEVER: IMPLICATIONS FOR CLINICAL AND BASIC SCIENCE

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There is considerable evidence that fever evolved as a non-specific host defence response to infection. Although physicians often treat "fever" as though it was a harmful manifestation of disease, this seems to be becoming less common. Within the past 30 years it has become increasingly clearer that during infection a fever is a highly regulated process, with both endogenous pyrogens and endogenous antipyretics being generated. Thus fever is a balance between fever-inducing agents (pyrogens) and fever suppressing factors or cryogens (Table). With some exceptions, the pyrogenic factors and processes tend to be pro-inflammatory, while the cryogenic branch is primarily anti-inflammatory.

Pyrogens	Cryogens
Interleukin-1	Arginine Vasopressin
Interleukin-6	Alpha Melanocyte Stimulating Hormone
Interferons	Glucocorticoids
Tumor necrosis factor	Tumor necrosis factor
Macrophage Inflammatory Factor	Interleukin-10
Prostaglandin E <sub>2</sub>	Epoxyeicosatrienoic acids (EETs)

Although the metabolism of arachidonic acid (AA) is generally thought to be pro-inflammatory, primarily via the production of prostaglandins and leukotrienes, there is now compelling evidence that metabolism of AA via cytochrome P-450/epoxygenases produces both antipyresis and reduction of inflammation. Four kinds of data demonstrate that P-450 is involved in antipyresis/anti-inflammation: (i) treatment with inhibitors of P-450 causes larger fever (Nakashima et al., 1996; Kozak et al., 1998); (ii) inducers of P-450 prevent fever (Kozak et al., 2000) and suppress lung inflammation due to intratracheal instillation of LPS (manuscript submitted); (iii) P-450 epoxygenase-derived eicosanoids (EETs) suppress fever (Kozak et al., 2000); (iv) EETs suppress expression of adhesion molecules on endothelial cells (Node et al., 1999). We believe that investigating fever and endogenous antipyresis will provide clinicians with additional mechanisms to modulate inflammation.

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## INVOLVEMENT OF THE PARABRACHIAL NUCLEUS IN COLD-INDUCED THERMOGENESIS IN THE RAT

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The parabrachial nucleus (PBN), an integrative site for the autonomic nervous system in the brainstem, is a target of neurons mediating cold information in the spinal dorsal horn. Many Fos-positive cells are observed in the PBN during cold exposure. These findings suggest the involvement of parabrachial neurons in the thermoregulatory system to maintain the body temperature in a cold environment. Thus, to test this possibility we investigated the effects of electrical stimulation of the PBN on  $O_2$  consumption ( $VO_2$ ) and those of electrolytic lesions of these regions on cold-induced thermogenesis. For stimulation experiments, male Wistar rats were anesthetized with urethan (1.2 g/kg, i.p.) and kept on a heating pad to maintain their body temperature at 36-37 °C. A concentric electrode was stereotactically inserted into the unilateral PBN region. Stimuli were 20 Hz monophasic square pulses with a duration of 0.5 ms and a strength of 10-40  $\mu$ A for 5 min.  $VO_2$  was measured by an open-circuit method. After the experiments, the stimulation site was verified histologically on the coronal section of the brain. Electrical stimulation of the PBN (20  $\mu$ A) immediately increased  $VO_2$  by  $1.26 \pm 0.11 \text{ ml/min/kg}^{0.75}$  (n=4) within 5 min, and  $VO_2$  returned to the baseline level within 25 min. The magnitude of thermogenesis increased with the intensity of the stimulus (10-40  $\mu$ A). The effective site was located in and around the medial or lateral PBN. For lesion experiments, a monopolar stainless-steel electrode was inserted into the PBN under anesthesia with ketamine (50 mg/kg, i.p.) and 1% isoflurane in air. A battery-operated transmitter was implanted intraperitoneally in each rat to measure body temperature ( $T_b$ ) and locomotor activity by a telemetry system. The measurement was performed at least 1 wk after the surgery. After the experiments, rats were anesthetized with Nembutal (50 mg/kg, i.p.) and the brain was fixed in formalin solution. The site and extension of lesion was examined histologically. Rats were placed in a metabolic chamber at the ambient temperature of  $28.5 \pm 0.1$  °C. The chamber was then cooled to  $16.6 \pm 0.6$  °C within 40 min and maintained at this temperature for 90 min. In rats with bilateral lesions in the PBN, cold stimulation elicited an integrated increase in  $VO_2$  of  $429.3 \pm 40.5 \text{ ml/kg}^{0.75}$  (n=11), which was significantly smaller than that elicited in the sham rats ( $679.6 \pm 35.0 \text{ ml/kg}^{0.75}$ , n=7). Cold exposure had no effect on  $T_b$  of sham-operated rats but decreased that of PBN-lesioned rats by  $2.14 \pm 0.12$  °C (n=11). Both frequency and duration of locomotor activity during the cold exposure were similar between the PBN-lesioned and sham-operated rats. The present study showed that electrical stimulation of the PBN elicited thermogenesis and that lesions in the PBN attenuated the thermogenesis during the cold exposure and resulted in a marked hypothermia. Accordingly, the PBN is involved in the neural mechanism of heat production against a cold exposure.

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## COLD-GATED CHANNEL AS A THERMOSTAT AGAINST COLD

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Cooling of skin evokes afferent impulses in cold fibers, which would elicit heat production (HP) responses (e.g., shivering) and/or heat-gain (HG) behaviors. In physiology, it has been assumed that a cold fiber is a sensor to transduce  $T$  into the firing rate (FR) code, with which the brain detects  $T$ . If a cold fiber is a sensor,  $T$  and FR must be in a one-to-one ratio. However, due to threshold and overshoot responses in FR,  $T$  and FR are not in a one-to-one ratio, and a cold fiber may not be a sensor. In contrast, from the threshold responses in FR, we have proposed that a cold-receptor itself is a thermostat that compares  $T$  with the threshold temperature and elicits impulses to drive HP responses or HG behavior when  $T$  is below threshold. However, the machinery of the thermostat is not clear. The aim of this study is to clarify it by analyzing ionic basis of cold receptors with patch-clamp techniques in cultured cells of dorsal root ganglion (DRG) containing cell bodies of sensory fibers. Wistar rats (2-14 days old) were anesthetized by diethyl ether and decapitated to isolate DRG. After dissociation with collagenase and trypsin, DRG cells were plated on a coverslip and cultured in DMEM containing 10 % fetal bovine serum. After identifying cold-sensitive neurons with Fura-2 microfluorimetry, we performed patch-clamp recordings in these neurons (EPC-7, List). Data were acquired with MacLab (AD Instruments). In whole-cell current-clamp mode, cooling transiently elicited receptor potentials leading to brief impulse trains. Because  $T$  and these responses were not in a one-to-one ratio, these cold-sensitive neurons may not act as sensors, but act as thermostats. In whole-cell voltage-clamp mode, cooling transiently induced non-selective cation currents, underlying the receptor potentials. In outside-out patch mode, cooling-induced single channel currents were recorded, indicating that these channels were ionotropic receptors responding to cold directly without cytosolic soluble substances. We conclude that the cold-gated channel itself is a thermostat molecule acting against cold.

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## THE EFFECT OF PEDALING RATE ON THERMOREGULATORY RESPONSES TO DYNAMIC CYCLE EXERCISE IN HUMANS

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Heat The heat loss response during dynamic exercise is important for the control of internal temperature. Work efficiency during a cycle ergometer exercise depends on pedaling rate, and the heat produced at a given work load during such an exercise differs with pedaling rate; thus, the pedaling rate while cycling may influence the thermoregulatory response during dynamic exercise. This study examined the effect of pedaling rate on heat loss responses in humans during a dynamic cycle ergometer exercise. Seven healthy male subjects performed on a cycle ergometer at low (L: 45 rpm) and medium (M: 75 rpm) pedaling rates at a constant work load (110 W) for 40 min. These experiments were performed in random order, and conducted at an ambient temperature of 25 °C and a relative humidity of 50% with minimum air movement. Heart rate, rating of perceived exertion, and oxygen uptake were significantly greater in condition M than in condition L. Mean arterial pressure did not differ between the conditions. Esophageal temperature did not differ with the pedaling rate during the exercise, while mean skin temperature 20 min after the onset of exercise was significantly lower in M than in L. Although sweating rates and the skin blood flow on the chest and forearm during the exercise did not differ markedly between L and M, the sweating rates on the thigh and palm were significantly greater in M than in L. Furthermore, the mean sweating rate of three parts (chest, forearm, and thigh) of the body tended to be greater in M than in L during the exercise. In addition, the slope of the relationship between esophageal temperature and sweating rate on the thigh tended to be greater in M than in L. Thus, total heat production during the exercise was greater in M than in L, while  $T_{es}$  did not differ with pedaling rate, indicating that the degree of heat loss during exercise may be greater in M than in L. Especially, this difference between pedaling rates is shown in sweating rate on the lower sites of the body. These results indicate that pedaling rate during dynamic cycle exercise influences both heat production and heat loss, and that these parameters increase with a rise in pedaling rate.

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## HYPERTONIC SALINE INJECTION ACTIVATES HEAT ESCAPE/COLD SEEKING BEHAVIOR VIA CENTRAL V<sub>1</sub>-RECEPTOR IN RATS

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Hypertonic saline injection activated heat escape/cold seeking behavior in rats (Nagashima et al., 2001), although the mechanism is still obscure. We speculate that arginine vasopressin (AVP) is involved in the mechanism via V<sub>1</sub>-receptors in the brain. Therefore, we tested the hypothesis that a cerebroventricular administration of V<sub>1</sub>-receptor antagonist attenuated heat escape/cold seeking behavior in rats. A biotelemetry device (15 x 30 x 8mm) for a core temperature (Tcore) measurement was placed in the abdominal cavity for each rat (male crj-Wistar rats, n = 14, body weight 350 ± 5 g (means ± SE)) under intraperitoneal anesthesia with sodium pentobarbital (5 mg/100 g•body wt), and a chronic cannula for a vehicle injection to the right lateral ventricle was implanted. In addition, the major salivary glands were removed to minimize evaporative heat loss. After a two-week recovery, rats were trained an operant behavior three times: Each rat was placed in an experimental box (50 x 10 x 30cm) in the heat of 40°C, and rats could get a cold air reward of 0 C for 30 s when moved in the specific area of the box. The rats learned moving periodically in and out the area to get the cold-air reward. At least 4 days after the training session, either 400 pmol/μl/100g•body wt V<sub>1</sub>-antagonist, [beta-mercaptopro-beta, beta-cyclopenta-methylenepropionyl<sup>1</sup>, O-Me-Tyr<sup>2</sup>, Arg<sup>8</sup>]-vasopressin, or the same amount of normal saline was injected via the ventricular cannula (ANT(+) and ANT(-), respectively). Thirty minutes after the ventricular injection, either hypertonic (2500 mM, HS) or normal saline (154 mM, NS) of 1 ml/100 g•body wt was subcutaneously injected. Then, the rats was placed in the operant system kept at 26 °C until Tcore was stabilized, and exposed to 40 °C heat for another 2 h. The same experiment was repeated by injecting another tonicity of saline for the same rat with a one-week interval. Baseline Tcore was lower in ANT(-)/HS group than ANT(-)/NS group (P<0.05, 36.5 ± 0.2 and 37.4 ± 0.1 °C). In contrast, the Tcore was higher (P<0.05) in ANT(+)/HS group (37.4 ± 0.1 °C) than ANT(-)/HS group. At the end of 2-h heat exposure in the operant system, Tcore was similar between ANT(-)/HS and ANT(-)/NS (37.5 ± 0.2 and 37.6 ± 0.1 °C) with greater number of the operant behaviors (P<0.05, 57 ± 4 and 41 ± 2). Moreover, Tcore in ANT(+)/HS group (38.5 ± 0.2 °C) was higher (P<0.05) than ANT(-) /HS group with less number of the operant behaviors (P<0.05, 42 ± 2). There was no difference in Tcore and the operant behaviors between ANT(-)/NS and ANT(+)/NS group (37.6 ± 0.2 °C, 40± 2). From these results, hypertonic saline injection activates heat escape/cold seeking behavior. Further, central AVP is involved in the mechanism for the activation of behavior via central V<sub>1</sub>-receptors. We surmize that the activation of heat escape/cold seeking behavior is one of heat-defense mechanisms especially in dehydrated condition.

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## AN HYPOTHESIS REGARDING A KEY ROLE OF ALTERATIONS OF BODY HEAT CONTENT IN THERAPEUTIC EFFECTS OF PHYSICAL THERAPY AGENTS

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Commonly used physical therapy agents (PTAs) are heat, electricity, light, massage, exercise, water. They have a therapeutic effect (TE) in patients with very different diseases. Why? Because, at least: (1) different diseases can have something common in their pathogenesis; (2) different PTAs can have something common in mechanisms of their influence. What is this common in mechanisms? To exert an influence on the organism, PTAs need to transfer an energy into the body; there are no body's reactions without this energy intake. What kinds of energy are to be transferred by PTAs? Almost always, these are thermal, electromagnetic, and mechanical ones. When absorbed by body tissues, thermal energy simply heats them (either this heating is registered or non-registered by our tools – no matter, in principle; anyway it takes place!). Electromagnetic and mechanical energies, being absorbed by tissues, have there some work to do; it relates to dislocations/shifts/recharges of microstructures. This work is inevitably accompanied with dissipation of a part of the energy as a heat. What is more, all non-dissipated energy will obligatorily be converted, sooner or later, in the most degraded form of energy – thermal one. Thus, any influence of PTAs is leading to a visible or invisible, immediate or delayed alteration of heat content of the body (AHCB). According to the principles of thermal physiology, a perturbing heat must only be taken off the body using appropriate reactions of thermoregulation. Body heat exchange is dependent on even small inside and outside temperature perturbations (especially within thermoneutrality zone), and there is the fact of convergence of temperature signals to integrating neurons that gather an information from large areas of the organism (Ivanov, 1990). How is this related to a TE of PTAs? I have hypothesized the following four stages of a PTAs TE appearance (Korobov, 1999): (1) any PTAs impact is accompanied by a transient AHCB; (2) due to an AHCB, appropriate thermoregulatory responses have been launched; (3) vital functional systems (cardiorespiratory, neural, endocrinological, bioenergetic) become involved in the reaction since the thermoregulatory system uses them to realize its effector activity; (4) as a result of a number of AHCB (i.e. – of thermal adaptation), a beneficial modification (optimization) of activity of the vital systems takes place including processes of salutogenesis. As a possible way of interrelation between a pathogenesis and thermoregulatory alterations, the phenomenon of depressing the thermoregulation using hypoxia (Giaja, 1938) may be instanced. Based on the fact that hypoxia is an attribute of any pathological process, and assuming that thermoregulatory reactions can, on the contrary, exert an effect on hypoxia, we may expect a TE of PTAs thermal stimulatings. In conclusion, it may be hypothesized that a transient AHCB is the primary and prime act of developing a TE of all known PTAs.

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## ENVIRONMENTAL CONTROL OF SWEATING MECHANISMS: MODIFICATIONS BY THERMAL ACCLIMATIZATION AND PHYSICAL TRAINING

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In the present paper, the following findings on <sup>(1)</sup>an overview of central and peripheral mechanisms of thermal and sweating regulation (Kosaka et al, 2001), <sup>(2)</sup>modification of sweating activities resulting from short- and long- term heat exposure (Lee et al, 1997), <sup>(3)</sup>effect of cold acclimation on sweating activities (Kosaka et al, 1988) and <sup>(4)</sup>modification of sweating activities by long-term physical training (Yamauchi et al, 1997) are reported from the concept of thermal adaptation. Namely, sweating is a heat loss response that is critical for improved physical performance and safety in extremely hot conditions. It is centrally regulated by the preoptic area and anterior hypothalamus(PO/AH) and peripherally transmitted by sympathetic sudomotor innervation, with acetylcholine as the primary neuroglandular transmitter. Modification of sweating activity through heat exposure or physical training is a physiological tactic for improved tolerance when individuals are challenged with exogenous or endogenous heat. A short-term heat challenge produces a lower resting and slower increase in body temperature as well as enhanced sweating response, while long-term heat exposure results in decreased sweat output. Cold acclimation results in reduced thermoneutral and skin temperature, lowered cold sensation, and reduced metabolic heat production. Physical training induces higher sweat output by means of greater sweat output per activated sweat gland, and a higher rate of skin blood flow.

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## APPROACHES TO MONITORING THERMAL STATUS IN HUMANS UNDER NONUNIFORM HEATING/COOLING ON THE BODY SURFACE

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Nonuniform temperatures on different parts of the body surface are often encountered during various conditions in space as well as in medical and occupational circumstances on Earth. In such cases, the primary challenge is how to best manage body comfort and safety with the information obtained by monitoring core and skin temperature. Findings from our research program have shown that traditional methods of monitoring body thermal status are not adequate in such conditions; usual measurement sites are not informative, and the relationship between the coefficients of core and skin temperature for averaging body temperature are not correct. Compared to uniform thermal conditions, the powerful influence of simultaneous cold and warm applications on different parts of the body surface significantly changes the response latency of the core, for example, rectal temperature. Moreover, nonuniform temperatures applied to the right and left sides of the head, respectively, result in a rapid and differential response in left and right ear canal temperatures. Therefore, this traditionally used site for making decisions about adding or removing body heat to achieve and maintain safety and comfort of personnel in Space and in other environments will provide incorrect information if only one side of the body is monitored. A plastic tubing liquid cooling/warming garment (LCWG) was designed in our laboratory with the capacity to differentially cool/warm different body zones. Through this experimental paradigm, our overall goal has been to achieve a better understanding of how to manage nonuniform thermal conditions while astronauts are engaged in extravehicular activities or in various onboard situations, with applications for Earth purposes. A further objective is to evaluate the efficiency of heat transfer from different body areas to identify the most effective zones to minimize the surface coverage by the LCWG, thus reduce energy consumption of the system, and precisely control body thermal status under such nonuniform thermal influences. Compared with temperature data from other body zones, findings demonstrated that the most informative method of assessing total body thermal status was by monitoring the thermal profile of the phalanges. This area vividly reflected the dynamic processes of heat dissipation or storage developing within the body. The marked changes in finger temperature amplitude and in blood perfusion intensity under nonuniform thermal conditions indicate the usefulness of the fingers to precisely measure alterations of heat balance in the body, predict changes in thermal status, and provide an alert for countermeasures to deal with a growing heat deficit or heat accumulation. The implications of this research for the development of an automatic feedback system to control thermal status and comfort of astronauts in space and occupational personnel on Earth are discussed.

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## **EVALUATION OF THE THERMAL PROFILE OF HUMAN FINGER PHALANGES AS A POTENTIAL SITE TO MONITOR BODY HEAT BALANCE**

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The goal of this research program is to maintain comfort and safety of astronauts/cosmonauts in thermal conditions that are difficult to monitor and control, such as nonuniform temperatures influences on the body surface during extravehicular activities. Prior research demonstrated that in sagittally divided nonuniform thermal conditions on the body surface, there were no significant differences in finger temperature between the two hands; both were responsive to a growing deficit in body heat (Koscheyev et al., 2000a). Consistent relationships also were evident between the core and fourth finger temperatures under thermal applications to nonsymmetrical body surface areas, further indicating the potential effectiveness of the fingers for placing a monitoring/controlling device (Koscheyev et al., 2000b). A series of studies was carried out in collaboration with the International Scientific Center "Arktika", Magadan, Russia to evaluate the specific site on the finger that would be most effective for placing a controller-sensor to initiate an automatic thermal feedback system in the space suit to maintain thermal homeostasis. Ninety seven male volunteers ages 19-23 participated in this research. The method of thermography (Raduga-MT4 thermovisual camera) was used to study the hand under temperature applications to the contralateral hand or each foot, respectively, to evaluate the thermal response on different fingers and the entire hand. Temperature changes on 20 sites of the hand were observed, including each phalanx, several points on the dorsal side of hands, and on the wrist area. The findings indicated that in spite of weak and distant thermal applications, a stable and uniform response to such thermal influences occurred on the entire fourth and fifth fingers, and on the distal and medial phalanges of the second and third fingers ( $p<0.05$ ). The thumb was not highly responsive to such thermal applications. The large range of finger temperature changes on the skin of the fourth and fifth fingers compared with other areas of the hand under different thermal conditions on proximal and distal areas the body surface indicates that the fourth and fifth fingers have the potential to be highly effective in precisely monitoring thermal changes in the body, predicting changes in thermal status, and can be utilized to initiate preventive countermeasures for a growing heat deficit or heat accumulation.

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## A POSSIBLE MECHANISM FOR NORADRENALINE INVOLVEMENT IN THE EFFECTOR RESPONSES TO COLD EXPOSURE

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It has been long known that the sympathetic nervous system mediator noradrenaline (NA) is involved in the response to cold. However, the mechanisms of NA participation in these physiological processes remain unclear. An attempt is made to summarize the results obtained in our experiments on human subjects and anaesthetized (nembutal, urethane) rats. The data concern the effect of NA on impulse activity of the central and peripheral thermosensors, thermosensitivity in human, changes in the thresholds and the intensity of cold-defense responses to cooling resulting from a specific route of NA administration, iontophoresis to the cooled skin surface, where thermoreceptors are concentrated. Data on changes in the immune response to antigen under the effect of NA in the cold and thermoneutral conditions are also reviewed. Based on the summarized data, a scheme for NA involvement in the formation of the effector (cold-defense and immune) responses to cold exposure is suggested. NA affects both the peripheral and central thermosensors. A decrease in the activity and sensitivity of the high frequency skin cold receptors presumably results in a decrease in cold sensation. An increase in the static and dynamic activities of the low frequency cold receptors and a moderate increase in the sensitivity of the neurons of the medial preoptic area of the hypothalamus in the low temperature range may produce a decrease in the threshold and an intensification of the thermoregulatory responses during cooling, as well as a considerable stimulation of the antigen binding function of the immune response during deep cooling, which is suppressed in the absence of NA. Intensification of the effector thermoregulatory and immune responses may be also related to the direct NA effect on the effector organs and tissues. The regulatory effect of NA on the effector (thermal-defense and immune) responses appears to be dependent on many factors: its relative concentration in the periphery and center, in the brain, and skin, where the bulk of the thermosensors is localized, and blood supplying the effector tissues.

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## NEW INSIGHTS INTO FETAL AND NEONATAL THERMOREGULATION

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Fetal animals appear to be thermally protected from heat and cold stress, by strategies employed by the pregnant animal during her own thermoregulatory responses, or by virtue of the fetus' thermal inertia. During experimental mild to moderate heat or cold exposure, or during exercise of the mother animal, the body temperature of fetal lambs, for instance, changes relatively less than does body temperature of the mother, with the feto-maternal thermal gradient being adjusted appropriately. What is not known, however, is whether fetal thermal protection is sustained in animals in natural conditions, where wide ambient temperature fluctuations, and variable solar radiation, wind and humidity occur. We have studied pregnant Angora goats (*Capra hircus*) in laboratory conditions as well as in their natural habitat, to examine the differences in fetal body temperature regulation. We used miniature dataloggers implanted intra-abdominally and under Fluothane (Halothane, Hoechst) anaesthesia, in mother and fetal animals for both laboratory and field experiments. Pregnant goats show greater variability of body temperature in natural as compared to laboratory conditions, but apparently continue, by physiological means, to reduce the corresponding variations in their fetuses. At birth, in natural conditions, body temperature of the delivered kid plummets more than in controlled laboratory conditions, and survival in this species is dependent on the prevailing environmental conditions, with the risk highest in conditions with low solar radiation. While abdominal temperature may be kept relatively constant in fetal animals, our measurements of brain temperature in fetuses using chronically implanted thermistors suggests that the temperature of the highly metabolic brain may vary in a fashion different to that of the rest of the body. These variations by have consequences for fetal development, and neuronal injury at birth. Maternal fever poses considerable thermal risk for the fetus (Laburn *et al* 1992). We have shown that bacterial products present in the fetal lamb circulation, and particularly in the intra-uterine cavity of the sheep (*Ovis aries*) result in abortion in between 50-75% of pregnancies. Fetal lambs themselves apparently are not capable of generating febrile temperatures *in utero*, although serum iron concentrations of fetuses fall significantly after Gram-positive pyrogen injection into the fetal circulation. Fever in the newborn and young animal can be deleterious; we report that repeated febrile episodes in young guinea-pigs (*Cavia porcellus*) are associated with growth retardation, at least partly as a result of decreased food intake during the febrile period.

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## SUBJECTIVE PERCEPTION OF COLD ADAPTATION, EXERTION, AND STRESS DURING A TWO WOMAN LONGITUDINAL TRAVERSE OF ANTARCTICA

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Adaptation to extreme cold involves both physiological and psychological processes. The subjective criteria for evaluating the magnitude of thermal sensations likely change with extended exposure to an extreme environment. Judgments of cold and thermal comfort may also interact with perceived level of physical exertion, and stress and coping mechanisms. Two women with prior polar exploration experience, ages 45 (American) and 47 (Norwegian), respectively, are engaging in a 3840 km, approximately 100 day longitudinal ski trek across Antarctica from Queen Maud Land to the Ross Ice Shelf, pulling sleds weighing 114 kg. Baseline measures included body composition, personality characteristics, stress and coping mechanisms, and performance expectations. During the expedition, each team member independently completed a twice weekly rating form assessing outside temperature and wind velocity; subjective perceptions of cold magnitude, body areas relatively coldest and warmest, physical exertion, energy level; and caloric intake. Measures of sleep quantity and quality, mood, appetite, feelings of boredom and monotony, stress and coping, work performance, and confidence about the successful completion of the expedition were also obtained. To ensure rating accuracy, equivalent English and Norwegian versions of the form were developed. The findings are presented in terms of the trajectory and range of perception of cold adaptation over time in relation to objective indices of temperature, wind velocity, caloric intake, and adiposity, and subjective measures of physical exertion and energy level, stress, and work performance. Objective vs. subjective indices of other variables such as caloric intake and appetite, wind velocity and extent of being bothered by the wind are compared.

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## NUMERICAL SIMULATION OF THE DYNAMIC THERMAL PHYSIOLOGICAL COMFORT OF A CLOTHED HUMAN BODY

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This paper reviews the methodology of numerical simulation of the dynamic thermal responses of human body and clothing and discusses the influence of various properties of clothing materials on the dynamic thermal comfort and sensations. The conventional mathematical models describing the heat transfer and moisture transfer processes are the basic energy and mass conservation equations, which follow Fourier's law and Fick's law respectively. The two transfer processes are considered essentially independent with each other. From the two equations, two fundamental criteria are generated to describe the thermal properties of clothing material, i.e. thermal resistance (Clo) and water vapor resistance ( $i_m$ ), which have been widely used in modeling the thermal comfort and/or thermal stresses of a clothed human body. However, the heat and moisture transfer processes are not independent with each other in clothing materials and at skin surfaces as they are coupled by the phase changes of water and absorption/desorption of water vapor by the fibers. A mathematical model describing the coupled heat and moisture transfer processes was developed, in which the dynamic sorption kinetic of fiber was taken into account. This model is able to illustrate how the moisture sorption capacity (called hygroscopicity) of clothing material influence the thermal and moisture comfort and sensations in various transient conditions where insensitive perspiration and dry environment are the dominant features. For extremely cold environmental conditions, the temperature difference between the body and external environment is huge so that heat transfer by radiation becomes very significant. A mathematical model has developed to take into account the radiation effect on the basis of the previous models. Using the model, the temperature and moisture profiles in clothing can be calculated to illustrate how different fibers and fabric materials influence the thermal comfort and moisture sensations in cold conditions. Besides, the liquid transport process in clothing cannot be neglected as a wearer may be often exposed to wetted situations due to sweating and/or raining/snowing. A mathematical model has been developed recently to describe the dynamic interactions between heat transfer by conduction and moisture transfer by diffusion, sorption/desorption, water evaporation/condensation and capillary actions. With specification of boundary conditions of the temperature and humidity at the clothing-skin and clothing-environment interfaces, the dynamic changes of the distribution of the temperature, moisture contents in the air and fibers of clothing and the volumetric fraction of the liquid water throughout the fabric can be calculated. This model is particularly useful in simulating the thermal comfort and sensations under sweating situations and/or externally wetted conditions and illustrate how the liquid moisture transport behavior of clothing (called moisture management) effect the thermal functional performance of garments. To simulate thermal functional performance of clothing under complex wear situation of sweating in extremely cold environment such as ski, a mathematical model has been developed more recently to describe various dynamic coupling effects among the heat transfer by conduction and radiation and moisture transfer by diffusion, sorption/desorption, evaporation/condensation, liquidation/solidation and capillary actions. These mathematical models, which are solved mainly by numerical computation methods, can be utilized to study the thermal comfort and thermal/moisture sensations under various transient conditions and to analyze the heat (cold) stresses under hot (cold) environment for given clothing materials. More importantly, the models can be utilized as effective engineering design tools to optimize the thermal functional performance of clothing for intended wear situations, which is illustrated by a series of computational results with comparison of experimental observations.

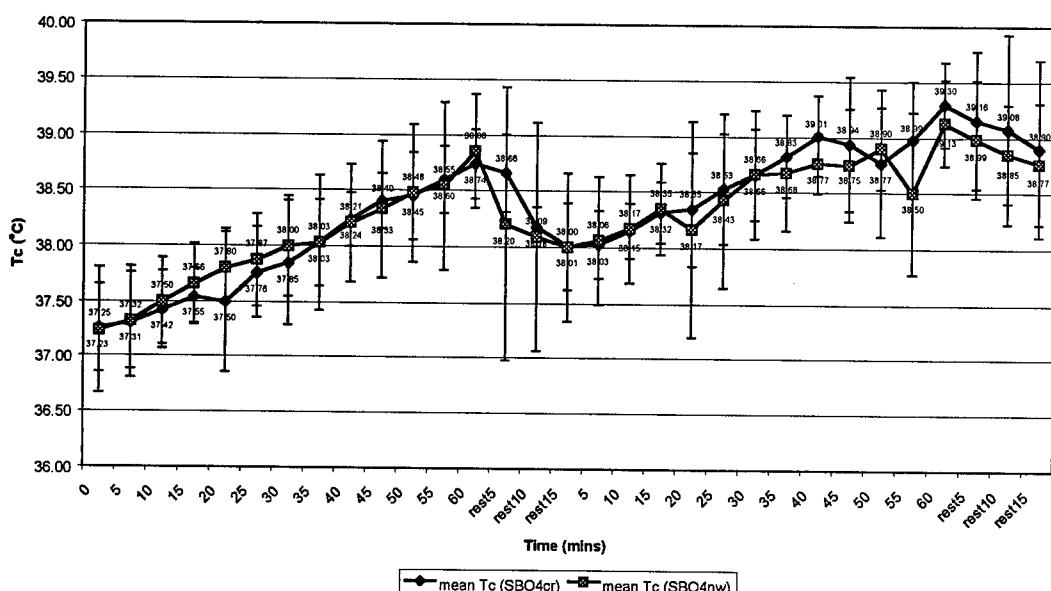
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## A COMPARISON OF TEMPERATURE REGULATION, FLUID EXCHANGE AND HEART RATE RESPONSE BETWEEN TWO LOAD BEARING SYSTEMS

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We evaluated temperature regulation and fluid exchange of first-year soldiers wearing two webbing and full-pack systems. Twelve volunteers performed two repeated trials wearing the current webbing (SBOcr) comprising of strap based system and a new vest webbing system (SBOnw). They were separated into two groups walking at speeds of  $4 \text{ km} \cdot \text{hr}^{-1}$  (n=7) and  $5 \text{ km} \cdot \text{hr}^{-1}$  (n=5) on a treadmill. The trials were conducted in a climatic chamber ( $33^\circ\text{C}$  dry bulb; 65% RH;  $850 \text{ W} \cdot \text{m}^{-2}$  radiation). They walked for two cycles of 60 min, with 15 min of rest. Another group of N=18 volunteers performed the trials wearing the webbing and with the respective current (FBOcr) and new (FBOnw) full-pack system. They performed trials at walking speeds of  $3.5 \text{ km} \cdot \text{hr}^{-1}$  (n=12) and  $5 \text{ km} \cdot \text{hr}^{-1}$  (n=6). Core temperature (Tc) in SBO trial ranged between  $37.1 \pm 0.4^\circ\text{C}$  and  $39.1 \pm 0.4^\circ\text{C}$  (SBOcr) and between  $37.1 \pm 0.5^\circ\text{C}$  and  $38.9 \pm 0.2^\circ\text{C}$  (SBOnw). There was no significant difference in mean Tc between SBOcr and SBOnw trials ( $P > 0.05$ ). In the FBO trial, Tc ranged between  $37.1 \pm 0.5^\circ\text{C}$  and  $38.8 \pm 0.7^\circ\text{C}$  (FBOcr) and between  $37.0 \pm 0.5^\circ\text{C}$  and  $39.1 \pm 0.5^\circ\text{C}$  (FBOnw). No statistical significance was reported. Mean heart rate (HR) in SBOcr trial ranged between  $115 \pm 11$  bpm and  $168 \pm 21$  bpm in the first cycle and between  $125 \pm 29$  bpm and  $169 \pm 17$  bpm in the second cycle. In the SBOnw trial, mean HR ranged between  $108 \pm 19$  bpm and  $165 \pm 19$  bpm in the first cycle and between  $120 \pm 27$  bpm and  $158 \pm 10$  bpm in the second cycle. Although not significantly different, the SBOcr trial recorded 5 to 11 bpm higher mean HR in the second cycle compared to the SBOnw trial. It could be concluded that the subjects needed greater physical effort to move with the SBOcr system after some degree of fatigue had set in. Mean fluid intake in the SBO trials was  $1.77 \pm 0.5$  L (SBOcr) and  $1.89 \pm 0.6$  L (SBOnw). In the FBO trials, mean fluid intake in the FBOcr and FBOnw trials were  $1.95 \pm 0.53$  L and  $2.35 \pm 0.61$  L respectively. The FBO system resulted in higher fluid intake compared to the FBOcr trial. Mean sweat rate (SR) in all the trials, including current and new load-bearing system (LBS), ranged between  $16 \text{ ml} \cdot \text{hr}^{-1}$  and  $19 \text{ ml} \cdot \text{hr}^{-1}$ , except for the two SBO trials at  $5 \text{ km} \cdot \text{hr}^{-1}$  which had means SR of  $25 \text{ ml} \cdot \text{hr}^{-1}$  and  $26 \text{ ml} \cdot \text{hr}^{-1}$ . The present study has found the LBSnw system to be an improvement to the LBScr system in terms of weight distribution. The volunteers responded similarly to both to the LBS systems for all factors, except for higher heart rate in the SBOcr trial, and they felt cooler when using the LBScr system. The level of heat stress was found to be similar between the two systems. The advantage of this study provided comparisons of the thermoregulatory responses to the existing and new webbing systems worn by the soldiers.

Mean $\pm$ SD of Core Temperature (Tc) in SBO when walking at  $4 \text{ km} \cdot \text{hr}^{-1}$  with 5% gradient



## ZYMOSAN-INDUCED FEVER: ROLE OF COMPLEMENT

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We have shown in previous studies that complement (C) is a necessary mediator of the febrile response of guinea pigs and mice to lipopolysaccharides (LPS), but not to muramyl dipeptide or poly I:C. However, these latter two exogenous pyrogens are weak stimulators of the C cascade. Zymosan (Zym), on the other hand, strongly activates C. It is also pyrogenic, probably, according to the available evidence, via induction of cytokines and prostaglandin E<sub>2</sub>, similarly to LPS. This study was undertaken, therefore, to determine whether C also is pivotal in the production of the fever evoked by this pyrogen. Zym injected intravenously (iv) at 0.5 mg/kg induced a monophasic, 1°C core temperature (T<sub>C</sub>) rise, with latency of *ca.* 36 min, peak at 88 min, and recovery at 180 min. Zym at 25 mg/kg, on the other hand, produced a quick-onset, *ca.* 1.1°C T<sub>C</sub> fall which reached its nadir at ~66 min; recovery was completed by 180 min. A second iv injection of 25 mg Zym/kg at 210 min yielded a smaller and briefer fall in T<sub>C</sub>, analogous to the effects of consecutive iv injections of 50 U of cobra venom factor (CVF, Sehic et al., 1998), a prototypic activator of the C cascade. The smaller response to a second injection of CVF is attributed to the depletion of C. CVF pretreatment (100 U, iv; C↓93%) 18 h before 25 mg Zym/kg converted this T<sub>C</sub> fall into a 1.1°C rise that persisted at this level for 92 min, then gradually returned to control over the following 60 min. These results suggest that Zym is inherently pyrogenic, but that this effect is manifested only when the dose of Zym is too small to activate C (*e.g.*, 0.5 mg/kg) or when C has been reduced by prior activation of the C cascade (*e.g.*, Zym at 25 mg/kg, 100 U CVF). Hence, C would not seem to be a mediator of the febrile response to Zym, but rather to its cryogenic effect.

Sehic, E., et al. (1998). *American Journal of Physiology*, 274, R1594-R1603.

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## PGE<sub>2</sub> SELECTIVELY ACTIVATES PERIPHERAL COLD-SENSITIVE NEURONS

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In response to exogenous pyrogen, immune cells generate endogenous pyrogen, leading to the production of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). PGE<sub>2</sub> may finally evoke heat production (HP) responses and/or heat-seeking (HS) behaviors, resulting in fever. However how PGE<sub>2</sub> acts on neurons is not known. Cooling the skin evokes afferent impulses in cold fibers, which may elicit HP responses and/or HS behaviors. PGE<sub>2</sub> receptors are abundant in dorsal root ganglion (DRG) containing cell bodies of cold fibers. Here we investigated effects of PGE<sub>2</sub> on cultured DRG cold-sensitive neurons with measurements of intracellular Ca<sup>2+</sup> ion concentration ([Ca<sup>2+</sup>]<sub>i</sub>) and patch-clamp techniques. Wistar rats (2-24 days old) were anesthetized with diethyl ether and decapitated to isolate DRGs. DRG cells were plated on coverslips (5?5mm), and cultured in DMEM at 37° in a humidified atmosphere containing 5% CO<sub>2</sub> for 1-3 days before recordings. Cultured cells on coverslips were loaded with Fura-2/AM (Donjindo), and were positioned in a recording chamber mounted on the stage of an upright fluorescence microscope (ECLIPSE E600-FN, Nikon). Cells were perfused with Krebs solution by gravity. Cell temperature was monitored with a thermocouple (0.3mm in diameter) close to cells. Cold stimulation was applied on cells by reducing temperature of perfusing solution from room temperature (26-28°) to 10-12°. [Ca<sup>2+</sup>]<sub>i</sub> in cultured DRG cells was recorded every 10s with a digital image analysis system (AQUACOSMOS, Hamamatsu). Cells which increased [Ca<sup>2+</sup>]<sub>i</sub> in response to cold stimulation were identified as cold-sensitive neurons. PGE<sub>2</sub> (10nM) induced an increase in [Ca<sup>2+</sup>]<sub>i</sub> in most (90%) of the cold-sensitive neurons but not in cold-insensitive neurons. PGE<sub>2</sub>-induced [Ca<sup>2+</sup>]<sub>i</sub> response was dose-dependent (EC<sub>50</sub>=2.8nM). When Ca<sup>2+</sup> was removed from the external solution, PGE<sub>2</sub>-induced [Ca<sup>2+</sup>]<sub>i</sub> response disappeared, indicating that the [Ca<sup>2+</sup>]<sub>i</sub> increase comes from extracellular Ca<sup>2+</sup> ions. In cell-attached patch recordings, PGE<sub>2</sub> directly evoked impulses in neurons showing PGE<sub>2</sub>-induced [Ca<sup>2+</sup>]<sub>i</sub> response. This suggests that PGE<sub>2</sub> receptors leading to cell excitation are present in cold-sensitive neurons. We concluded that immune signal selectively activates peripheral cold-sensitive neurons?even when it is not cold. This might evoke HP responses and/or HS behaviors to induce fever.

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## **THERMAL RESPONSES DURING STANDING AND WALKING AT DIFFERENT AIR VELOCITIES IN COLD**

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The aim of this work was to study how different air velocities affects thermal responses during standing and walking in cold. Eight young (21-25 years) male subjects were stabilized for 60 minutes at 20 °C. During the 30 min cold exposure the subjects either stand still or walked on the treadmill (2.8 kmh<sup>-1</sup>) towards the wind by two different exercise intensity. Exercise intensity was adjusted by changing the inclination of the treadmill between 0° (lower exercise intensity, metabolic rate 124 Wm<sup>-2</sup>, LE) and 6° (higher exercise intensity, metabolic rate 195 Wm<sup>-2</sup>, HE), thus keeping the speed of the body movements unchanged. Temperature in the wind tunnel was -10°C and air velocity was 0.2 ("still air", NoWi), 1.0 (Wi1) or 5.0 (Wi5) ms<sup>-1</sup> in separate measurements. The subjects wore Finnish military winter clothing with the basic insulation of ca. 2.2 clo. Skin (15 sites) and rectal temperatures, heat flux from the skin (8 sites), and oxygen consumption were measured. Wind increased convective heat loss, which was significantly higher, both at rest and during exercise, at Wi5 in comparison to NoWi and Wi1. At rest the heat flux increased already at Wi1 in comparison to NoWi. Walking increased convective heat loss only at NoWi in comparison to standing. Exercise intensity did not affect the mean heat flux at any air velocity. During exercise, mean skin temperature (Tsk) remained at higher level than during standing in all air velocities. The differences between the walking and the standing at the end of cold exposure were 0.6 (NoWi), 1.0 (Wi1) and 1.1 °C (Wi5) at LE, and 1.3, 1.6 and 1.7 °C at HE, respectively. The higher exercise intensity increased Tsk only at NoWi and Wi1 in comparison to LE. Both during rest and exercise, Tsk decreased significantly more at Wi5 than at NoWi and Wi1. Air velocity did not affect a peripheral cooling rate, judging from the finger temperature, at rest or at LE. At the end of HE the finger temperatures were significantly higher at NoWi and Wi1 than at Wi5. Oxygen consumption increased significantly during Wi5 at standing in comparison to NoWi and Wi1. The present results suggest that in windy conditions, during standing and walking at studied exercise intensities, the convective heat loss is dependent only on air velocity. The exercise-induced increase in Tsk is not accompanied by a higher heat flux. Increase of oxygen consumption during Wi5 at standing was probably due to shivering induced increase in metabolic rate.

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## SELECTIVE BRAIN COOLING AND THE CRANIAL ARTERIOVENOUS TEMPERATURE DIFFERENCE IN FREE-RANGING ORYX (ORYX GAZELLA)

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The arid-zone antelope, the oryx, is often cited as a prime example of an animal that benefits from selective brain cooling. Whether oryx employ selective brain cooling never has been investigated. We implanted miniature data loggers connected to thermistors into oryx (*Oryx gazella*) under etorphine- induced, and halothane (1-2%)- maintained, general anaesthesia. We measured the temperature of carotid arterial blood ( $T_{car}$ ) and the hypothalamus ( $T_{hyp}$ ) in two male and two female oryx every five minutes, to an accuracy of better than  $0.1^{\circ}\text{C}$ , over periods ranging from six to fifteen days during the southern hemisphere summer. The animals were ranging free in their natural habitat during data collection. Three of the animals used selective brain cooling as part of their daily thermoregulatory repertoire, usually in the late afternoon and evening at the peak of their nychthemeral rhythm, but apparently never during exertional hyperthermia. One male did not use selective brain cooling during the study period. Our hypothesis is that selective brain cooling serves to modulate thermoregulation, rather than to protect the brain from overheating. Implementation of selective brain cooling reduces hypothalamic temperature and therefore attenuates heat loss effectors. Conversely, cessation of selective brain cooling excites heat loss effectors. Respiratory evaporation ought to reflect in cooling of cranial blood, with respiratory heat loss proportional to the product of cranial blood flow and the difference between  $T_{car}$  and jugular blood temperature ( $T_{jug}$ ). In one male and one female  $T_{jug}$  also was measured. On average,  $T_{jug}$  was  $0.3 \pm 0.2^{\circ}\text{C}$  cooler than  $T_{car}$ , but there were times when  $T_{jug}$  was warmer than  $T_{car}$ . At high body temperatures  $T_{jug}$  was significantly cooler when the oryx were not using selective brain cooling than when they were, consistent with enhanced respiratory heat loss if cranial blood flow was not reduced concurrently. In fact, cranial blood flow increases as body temperature increases (Maloney & Mitchell 1997), with blood flow to the upper respiratory tract, including the nasal mucosa, accounting for the majority of the change (Hales 1973). Thus free-ranging oryx can employ selective brain cooling but we found no evidence that SBC was employed to protect a thermally vulnerable brain. Instead, cessation of selective brain cooling, at high body temperatures, increased respiratory heat loss. Our results concur with the putative role of selective brain cooling as a governor on water use for thermoregulation.

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## **EFFECTS OF SIMULTANEOUS CHANGES IN EXERCISE AND AMBIENT TEMPERATURE ON BODY HEAT BALANCE**

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The effect of simultaneous changes in exercise and ambient temperature on body heat balance and physiological strain were studied. The exercise/rest periods were either 10/10 minutes or 30/30 minutes, and the total duration of the protocol was 120 min. Exercise (walking 6 km/h on treadmill, slope 2°) was performed in cold environment (-15 °C, air velocity 2.5 m/s). The resting periods were spent sitting at +10 °C, air velocity 0.2 m/s, with the same clothing as during exercise. The subjects were 7 voluntary healthy young men. They were wearing Finnish military winter clothing (M91, thermal insulation about 2 clo) and rucksack (12 kg). During the rest periods drinking of water was allowed ad libitum. Data are given as mean  $\pm$  SE. The mean skin temperature during the 10/10 schedule was  $31.7 \pm 0.2$  °C and during the 30/30 schedule  $31.3 \pm 0.3$  °C. Deep body temperature was in average 37.5 °C during both schedules. At the end of the last exercise period oxygen consumption was  $33.5 \pm 0.9$  ml/min/kg in the 10/10 schedule and  $32.4 \pm 3.8$  ml/min/kg in the 30/30 schedule. During the exercise periods heart rate was in average 150 beats/min in both schedules. The amount of sweating was greater during the 10/10 schedule ( $809 \pm 118$  g) than during the 30/30 schedule ( $667 \pm 182$  g). Also the fluid intake was greater during the 10/10 schedule ( $457 \pm 121$  g) than during the 30/30 schedule ( $141 \pm 41$  g). In conclusion, the body heat balance and physiological strain were comparable in both exercise/rest schedules. The amount of sweating as well as fluid intake were greater during the 10/10 minutes exercise/rest schedule. This finding can be due to the fact that the number of rest periods was greater in the 10/10 schedule, and the transition from exercising in -15 °C to resting in +10 °C possibly promotes sweating. These findings suggest that specified instructions for clothing and fluid intake are needed for different combinations of exercise and rest in changing ambient temperatures.

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**THE ROLE OF POSTPRANDIAL HEAT PRODUCTION AND EXERCISE IN ADJUSTING  
SHIVERING THERMOGENESIS IN JAPANESE QUAIL CHICKS, *COTURNIX COTURNIX*  
*JAPONICA***

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Regulatory thermogenesis of birds is composed of shivering thermogenesis, and in cold-acclimated chicks possibly also of nonshivering thermogenesis. Obligatory thermogenesis by postprandial heat production and exercise are regarded as potential substitutes for shivering in cold. These thermal by-products of feeding and locomotion may be of benefit in energy sparing especially in juvenile birds if the energetic costs of regulatory and obligatory thermogenesis are not additive. In this study, the effects of postprandial heat production and exercise on shivering were examined first time at effector (muscle) level in young birds. In a first set of experiments, 8-day-old chicks were exposed to fasting for 31 h. Thereafter, oxygen consumption and shivering EMGs from pectoral and gastrocnemius muscles were measured at ambient temperatures between 33-12°C. At a thermoneutral temperature (33°C), heat production in fasted chicks was 39% lower than in ad libitum fed controls. The absolute difference between control and fasted chicks decreased with decreasing ambient temperature being at 12°C less than half of that observed at 33°C. Despite the lower metabolic rate, the amplitudes of shivering were higher in fasted chicks, especially in pectoralis. This indicates that fasted chicks used shivering to compensate the decrease in postprandial heat production. In the second set of experiments, the effect of exercise on thermoregulation of three-week-old chicks was studied at three different ambient temperatures (25, 15, and 0°C) during forced walking on a treadmill (speed 0.09 ms<sup>-1</sup>) and at rest. The shivering in pectoralis was suppressed within 20 s after the onset of exercise, at 25°C completely and at 15° and 0°C with a decrease of 20µV. In response to decreasing core temperature, chicks were capable of increasing shivering when walking. The physical strain of exercise, measured as oxygen consumption, was dependent on ambient temperature. Between 15°C and 0°C, a major increase occurred from 72.3 to 143.7 ml·min<sup>-1</sup>·kg<sup>-1</sup>. Due to shivering suppression and increased forced convection during exercise, hypothermia developed the faster the colder the ambient temperature was. Although exercise interacts with regulatory thermogenesis partially substituting it, the benefit of exercise, if any, is restricted to temperatures slightly below thermoneutrality. Japanese quails chicks are capable of replacing shivering in cold by postprandial heat production but exercise cannot be utilized in thermoregulation either in energetically or thermally favourable way.

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## ANALYSIS OF NEURONAL MECHANISM FOR BEHAVIORAL THERMOREGULATION IN RATS

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Homeothermic animals regulate their body temperature by using behavioral as well as anatomic processes. Behavioral thermoregulation means the behavior for looking for a better thermal environment, including wearing clothes and building houses in humans. While the brain mechanisms for the autonomic process is well documented, that for the behavioral thermoregulation has not been as well understood, partly because there was no appropriate experimental model. Chen et al., recently developed a new operant system for studying behavioral thermoregulation. In this system, a rat in a box of high load temperature can get a cold reinforcement for 30 sec when it moves into a specific area in the box. This system is based on rats' natural behavior and they easily learn the procedure. The purpose of the present study is to analyze the neuronal mechanism for behavioral thermoregulation using this system. In the first experiment, we analyzed the heat-escape behavior, and brain regions activated were surveyed by immunohistochemical analysis of c-Fos protein. Male specific pathogen-free Wistar rats (300-400g, Charles River Japan, Osaka, Japan) were used in this study. Under sodium pentobarbital anesthesia (50 mg/kg, *i.p.*), a biotelemetry device was implanted in the peritoneal cavity of each rat for the measurement of body temperature. After this surgery, the heat-escape experiment (40°C load temperature and 5°C reinforcement) was conducted for 3 hrs twice on separate days. Immediately after the last experiment, all the rats were deeply anesthetized with sodium pentobarbital and perfused with formaldehyde. The brains were removed and the whole brain sections were made for the immunohistochemistry analysis. In the rat performing heat-escape behavior strong Fos immunoactivity was found in the median preoptic nucleus (MnPO), the dorsomedial hypothalamus (DMH), and the parastrial nucleus as compared with the control. In the second experiment, the effects of the brain lesion or transection on behavioral thermoregulation were evaluated. As in the first experiment, each rat did heat-escape behavior twice. Then, the rat received electrolytic lesion of the MnPO, the DMH, or the amygdala or microknife transection of the stria terminalis. Ten days after the surgery, the heat-escape behavior was basically same in the number of getting reinforcement as that before the surgery in all the rats. These destroyed regions might not be responsible for the control of heat-escape behavior. Another possibility is that although they play some role for behavioral thermoregulation, the behavior is under the control multiple neuronal mechanisms working in parallel.

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## THE HUMORAL MECHANISM THAT ACTIVATES BRAIN PROSTAGLANDIN E<sub>2</sub> BIOSYNTHESIS DURING FEVER

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Fever is mediated through production of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) in the brain. To understand where and how PGE<sub>2</sub> is produced in the brain, we have been studying expressions of enzymes responsible for PGE<sub>2</sub> biosynthesis in the rat brain and its relevance to fever. In our typical experiment, rats were challenged with lipopolysaccharide (LPS, 0.1-0.4 mg/kg, i.p.). Five hours after the injection, their brain and cerebrospinal fluid were sampled for histological analysis and PGE<sub>2</sub> assay, respectively, under diethyl ether or pentobarbital anaesthesia (5 mg/kg). In some cases, rats were pretreated with NS-398 (4 mg/kg, i.p.), an inhibitor of cyclooxygenase-2 (COX-2), prior to the LPS injection. The results were summarized as follows. (1) COX-2, an inducible-type enzyme converting arachidonic acid to PGH<sub>2</sub>, was induced in brain endothelial cells in response to LPS (Matsumura et al. 1998). (2) COX-2 expression was correlated with fever in terms of timing and magnitude (Cao. et al. 1997). (3) Inhibition of COX-2 activity suppressed fever (Cao. et al., 1997). (4) Microsomal-type PGE synthase (mPGES), another key enzyme that converts PGH<sub>2</sub> to PGE<sub>2</sub>, was also induced in brain endothelial cells after LPS challenge. (5) mPGES was colocalized with COX-2 in the perinuclear region of the endothelial cells (Yamagata et al. 2000). (6) Inhibition of COX-2 activity suppressed PGE<sub>2</sub> level in the brain. (7) Endothelial cells are the only cell group that expresses both COX-2 and mPGES in the brain. (8) Cytokine receptors are expressed in brain endothelial cells. (9) COX-2 induction and PGE<sub>2</sub> elevation were not suppressed by bilateral vagotomy at the cervical level indicating that these responses are not vagally-mediated. (10) Even under untreated conditions, low amounts of COX-2 and mPGES have been already expressed in brain endothelial cells. These results strongly suggest that circulating LPS and/or cytokines act on brain endothelial cells, which, in turn, produce PGE<sub>2</sub> through inductions of COX-2 and mPGES. This seems to represent one of the humoral mechanisms of immune-brain communication that leads animals to fever.

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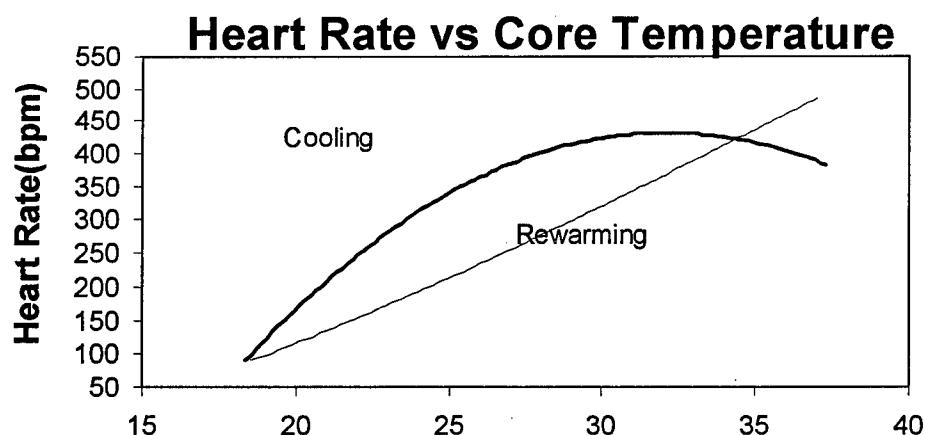
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## CORRELATIONS AMONG HEART RATE, CORE TEMPERATURE AND BLOOD PRESSURE IN TELEMETRY-EQUIPPED HYPOTHERMIC RATS

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Prior to using a rat model of hypothermia and rewarming to examine heart rate and blood pressure variability for potential autonomic signatures of hypothermia and rewarming, changes in core temperature (Tc), heart rate (HR), mean blood pressure (BP), and arrhythmias were defined. *Materials and methods:* Adult, male Sprague-Dawley rats had telemetry transmitters (Data Sciences, TL11M2-C50-PXT) surgically implanted (sodium pentobarbital 50 mg/kg, i.p. supplemented as needed with methoxyflurane to maintain anesthesia), and 2 weeks recovery were allowed prior to induction of hypothermia. On the day of data collection, rats were lightly anesthetized (sodium pentobarbital 35 mg/kg, i.p.) and placed in a coil of copper tubing through which temperature-controlled water was circulated. Four animals were each subjected to hypothermia twice with at least 4 days between exposures. Animals were cooled to a Tc of 19 to 20°C, maintained there for 30 min, and then rewarming. Tc, BP, HR from ECG and 10 sec strips of ECG waveforms were collected every 5 min throughout hypothermia and rewarming. *Results:* Rats were cooled at a rate of 0.126 °C/min and rewarming at 0.221 °C/min; during cooling both HR and BP declined after initial increases with the drop in HR starting at a higher Tc than the drop in BP. Similar findings have previously been reported in human patients. The correlation between HR and Tc as well as that between BP and Tc were different during cooling than during rewarming. The Figure illustrates the correlation between Tc and HR during cooling and rewarming for a total of 8 trial; for cooling  $y = -1.798x^2 + 115.5x - 1424$ ,  $R^2 = 0.8805$ ; for rewarming  $y = 0.1875x^2 + 11.02x - 178.8$ ,  $R^2 = 0.9117$ . A correlation between Tc and BP yielded the following equations for cooling  $y = -0.4214x^2 + 24.43x - 215.6$ ,  $R^2 = 0.6897$ ; for rewarming  $y = -0.1809x^2 + 12.78x - 88.02$ ,  $R^2 = 0.7412$ . In several of the trials at Tc < 25 °C the rats exhibited characteristic "J" or Osborn waves in the ECG. *Conclusion:* Thus the rats exhibited cardiac arrhythmias and other cardiovascular anomalies similar to those seen in human patients with severe hypothermia. Correlations such as these could be used in predicting physiological status under environmental extremes. These findings further validate the use of the rat for studying the pathophysiology of hypothermia and rewarming.



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## CAUDAL RAPHE NEURONS AND THERMOREGULATORY EFFERENT CONTROL

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The rat's tail is a major organ of heat loss. Its thermoregulatory function depends on blood flow, which is under sympathetic control. The central efferent pathways for this are poorly understood. Three lines of experiment were performed on urethane-anesthetized rats (1-1.5 g / kg, i.v. after surgery under 2 % isofluorane). In the first, microinjections of sodium glutamate were used to activate the cell bodies of sympathetic premotor neuron groups in the medulla, while sympathetic activity was recorded from postganglionic axons in the tail and, for comparison, simultaneously from the renal nerve. Neurons in the rostral ventrolateral medulla strongly excited the renal nerve but only weakly affected tail sympathetic activity. Conversely, medullary raphe neurons had little effect on the renal nerve, but strongly stimulated tail units (Rathner & McAllen, 1999). In a second series, a water jacket around the animal's shaved trunk was briefly perfused with cold rather than warm water, which lowered trunk skin temperature by 2-10  $^0$ C from resting warm conditions (35-40  $^0$ C). Repeated episodes also lowered core (rectal) temperature. Cooling of either core or skin temperature independently activated tail sympathetic fibre activity. This activation could be completely blocked by microinjecting the inhibitory amino acid, glycine (200 nl, 0.5 M), into the rostral medullary raphe (n=6). The critical area encompassed the nuclei raphe magnus and pallidus at the level of the caudal part of the facial nucleus. A third series was performed on rats anaesthetised as described above, but given bolus doses of pancuronium (2 mg/kg, i.v.) during recording periods. Paralysis was allowed to wear off between doses, and satisfactory anaesthesia confirmed by absent withdrawal reflexes. Single neurons were recorded from the same raphe region described above, and these were antidromically activated from the upper lumbar spinal cord (the level of the tail sympathetic outflow). A subset of these raphe-spinal neurons was reproducibly activated when the trunk skin was cooled. Taken together, these findings suggest that the sympathetic premotor neurons for thermoregulatory control of rat tail vessels reside in the rostral medullary raphe.

Rathner, J.A. & McAllen, R.M. (1999) Differential control of sympathetic drive to the rat tail artery and kidney by medullary premotor cell groups. *Brain Research*, 834, 196-199.

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## INHALATION REWARMING AND COOLING DOES NOT INFLUENCE BRAIN-STEM TEMPERATURE

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Inhalation rewarming is an effective method for eliminating respiratory heat loss. Numerous studies have also proposed that it is effective in enhancing the rate of rewarming of hypothermic individuals, but this view has been challenged by studies which have demonstrated that both in laboratory and simulated field settings, inhalation rewarming provides no improvement over spontaneous rewarming. The present study tested the hypothesis that inhalation rewarming may provide a thermal increment to central neural structures adjacent to the nasopharyngeal region, specifically the brain-stem, medulla and hypothalamus. In this manner, inhalation rewarming, though not capable of enhancing the rewarming rate of body core temperature, might act to stabilise the temperature and hence the function of vital structures in the central nervous system, responsible for respiration, cardiac function and temperature regulation. This hypothesis was tested by monitoring the auditory evoked brain stem responses (AEBRs) of fourteen subjects (7 male and 7 female) inspiring room air (24°C) followed by hot air (41°C) saturated with water vapour and cold dry air. The order in which the latter two conditions were presented to the subjects was counterbalanced. The latencies of peaks I, III and V, and the inter-peak latencies (IPLs) I-III, III-V, and I-V were compared between the three conditions with a repeated measures ANOVA. Changes in IPLs are sensitive makers of changes in brain stem temperature. The total duration of each condition was 25 minutes, and AEBRs were recorded during the last 10 minutes. Prior to the measurement of AEBRs tympanic temperature (Tty) was measured with an infra-red tympanic thermometer. There were no significant differences in Tty, peak latencies I, III, and V, and IPLs I-III, III-V, and I-V. The results indicate that inhalation of hot and cold air does not influence Tty, nor does it influence the temperature of the brain-stem. We conclude that inhalation rewarming is not capable of warming the vital central neural structures adjacent to the nasopharynx in any significant manner. Consequently, it appears unlikely that inhalation rewarming is an efficient means of reviving brain-stem and hypothalamic function in hypothermic victims.

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## LESSONS FROM THE PAST - HUMAN AND ANIMAL THERMAL PHYSIOLOGY

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Early attempts to establish the location of a thermoregulatory centre in the brain accounting for the stability of deep-body (core) temperature ( $T_c$ ) in homeotherms found their first landmark in 1912 when Barbour using a water perfused thermode identified a heat-sensing centre driving  $T_c$  in the direction opposite to the change of thermode temperature. The emerging mono-centric concept of hypothalamic thermoregulation encompassing both control and thermosensory functions was supported by clinical and pathological studies and firmly cemented in the 60s with many classical quantitative thermode studies and by the discovery of warm sensitive hypothalamic neurons. Only in the late 60's theoretical considerations began to question hypothalamic thermosensitivity (HTS) as being too low to account for the known stability of homeothermic  $T_c$ , a problem initially overcome by proposing the classical hypotheses of adjustable set point control and of multiplicative interaction between skin and hypothalamic temperature. Also in the 60s the discovery of spinal cord thermosensitivity as well as of extrahypothalamic vestigial controller functions within the central nervous system (CNS) paved the way for studies establishing the multiple-input, multiple-controller concept of thermoregulation by identifying further extrahypothalamic sites of temperature signal generation, whose contributions, when integrated as deep-body thermosensitivity, were shown to closely match the thermosensitivity postulated to explain the known stability of  $T_c$ . Early monocentric studies of thermoregulation during exercise were confronted with the observation of reduced HTS requiring substantial non-thermal inputs as extra drives for heat defence. With the multiple-input concept this hypothetic non-thermal input substituting for the reduced HTS could be fully replaced by the contribution of extrahypothalamic thermosensors. Parallel to these studies ideas on neuronal temperature sensing have greatly advanced from viewing bimodal peripheral thermoreceptors and hypothalamic warm- and cold-sensitive neurons as the only relevant signal generators towards a very complex picture including monomodality of peripheral warm and cold thermoreceptors and multimodality of deep-body thermosensors. Our concepts on thermosensory specificity have radically changed, and today it appears that the deep-body temperature signal is only in part provided by thermoreceptive afferents, while its major fraction is generated by interneurons that are for the most part warm sensitive. Predominance of multimodality among neurons generating thermal inputs within the CNS seems to contribute to the interactions between thermoregulatory and other homeostatic control systems that are increasingly elucidated. Fever as a natural disturbance of homeothermia has been an important corrective for our understanding of how  $T_c$  is regulated. That febrile  $T_c$  changes are regulated was discovered as early as 120 years ago. Starting in the 40s with the important distinction between exogenous and endogenous pyrogens, research into the latter has continued to disclose multiple interacting cytokines driving many cellular and humoral host defence activities with prostaglandins being an important mediator between cytokines and hypothalamic targets generating febrile hyperthermia. Previous views of the organum vasculosum laminae terminalis as a monocentric, virtually exclusive blood-to-brain interface for fever mediation are changing and very recent data support a multiple input system involving vagal and somatic afferents as putative pyrogen sensors.

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## AN EXPERIMENTAL MODEL FOR EXAMINING CHANGES IN SKIN TEMPERATURE IN THE HANDS AND FEET OF YOUNG AND ELDERLY SUBJECTS IN RESPONSE TO LOCAL COOLING

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An important component in the regulation of body temperature is skin blood flow, especially in peripheral sites such as hands and feet. Any impairment of vasomotor control in these skin areas can, in addition to causing tissue damage, compromise thermoregulation and may, under certain circumstances, be detrimental for health. While patho-physiological related changes in the control of skin blood circulation (usually reduced blood flow) are often clearly discernible, natural age related changes in the healthy elderly are less well documented and opinions vary concerning the degree and pattern of these changes. The object of this study was to design a reliable, repeatable and, non-invasive experimental method for examining how peripheral circulation in the extremities (hands and feet) is affected by a short period of local cold exposure and which can be easily applied to both young and elderly subjects. The experiments, which took place in a climatic chamber under thermoneutral ambient conditions ( $T_a$  26 -28°C), were carried out in 12 young male (mean age 25 years) and 8 elderly female and 4 elderly male (mean age 77 years) healthy volunteer subjects. During the experiments, the lightly clothed subject sat in a comfortable stool while resting either their hands or their feet (palm/sole down) on a thin grid made of nylon netting. Following a 30 minute control period to establish base line values (a generally vasodilated state with particular emphasis on the presence of thermal symmetry between the left & right sides of the body) the right hand or the left foot was immersed for a period of 2 minutes in 10°C water (a thin plastic bag was worn during the immersion period to avoid skin wetting). Throughout the experiments measurements of surface temperatures (infra-red thermal imagery and thermocouples) and skin blood flow (laser Doppler flowmetry) were made at multiple skin sites. Blood pressure and heart rate were also measured. Calculations were made of the time taken for skin temperatures in the 'cold' hand or foot to regain 80% of the cold induced drop in temperature (recovery time). None of the subjects found the experiments to be discomforting. The main findings were:- 1) Under thermoneutral ambient conditions skin temperatures on the hands and feet were lower in the elderly than in the young subjects. 2). Under thermoneutral ambient conditions skin temperatures on the feet were always lower than on the hands in both the young and elderly subjects. 3) Recovery time after cooling was always longer in the elderly subjects, both for hands and for the feet. 4) In both young and elderly subjects recovery time was always shorter for the hands than for the feet. The results clearly indicate that the peripheral responses to local cooling differ in the hands and feet and, in addition are altered with increasing age. The sensitivity of the method indicates that it may be a suitable model for the early detection of blood flow disturbances associated with peripheral arterial disease.

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## BRAIN, CAROTID ARTERIAL BLOOD, AND ABDOMINAL TEMPERATURES IN UNRESTRAINED BABOONS

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Baboons (*Papio ursinus*) are the only diurnal non-human primates to have colonized the open grassland savannas and arid sand plains of Africa. One hypothesis seeking to explain their success invokes selective brain cooling, dependent on evaporation within the large muzzle (Wheeler 1988), but no one has investigated whether baboons actually can employ selective brain cooling. Another potential mechanism is adaptive heterothermy; baboons living in the Namib Desert have a nycthemeral rhythm of body core temperature with amplitude that exceeds 3°C, which is increased to ~ 5 °C when they do not have access to drinking water (Brain & Mitchell 1999). We habituated baboons that originated from troops inhabiting the mesic southern boundary of South Africa to a constant-temperature environment (25°C) in an indoor animal house. We implanted fine thermistors, in guide tubes, into one carotid artery and into the brain, just dorsal to the hypothalamus, using ketamine (10 mg/kg i.m.) sedation, thiopentone sodium (4 mg/kg i.v.) induction and halothane (2% inhalation) anaesthesia. The leads from the thermistors were tracked subcutaneously to miniature thermometric data loggers in the baboons' abdominal cavities. We also inserted a logger in the abdominal cavity itself. All loggers had a calibrated accuracy of <0.1°C. After recovery from surgery, the baboons were transferred, in pairs but in separate cages, to a climatic chamber where we could control dry-bulb temperature and humidity, and impose a 12-hour (06:00 to 18:00) light/dark cycle. Baboons were fed and their cages cleaned once a day, but otherwise were disturbed as little as possible. They were exposed for seven consecutive days to a constant benign environment (23°C, 12 g/m<sup>3</sup> absolute humidity), and also to a cyclic environment which was ramped from 15°C, 9 g/m<sup>3</sup>, at 08:00 to 35°C, 15 g/m<sup>3</sup> at 10:00, and then back to starting conditions between 15:00 and 17:00. Mean radiant temperature was equal to air temperature, and wind speed was <0.5 m/s. For two of the days, in both the constant and the cyclic environment, water was withheld from the baboons, and fruit removed from their diet; on all other days they had water *ad libitum*. Carotid artery and abdominal temperatures were similar, and showed a nycthemeral rhythm with acrophase around mid-day, and a trough-to-peak amplitude of about 1°C in the 23°C environment. The amplitude was increased by diurnal heat stress, without nocturnal temperatures being affected. The amplitude was more than doubled by the combination of diurnal heat stress and water deprivation, but did not attain that exhibited by dehydrated *P. ursinus* in the extreme Namib Desert environment. Brain temperature never was less than arterial blood temperature, and reached 40°C in the heat-stressed dehydrated baboons. *P. ursinus* therefore does not appear to have the capacity for selective brain cooling. The baboons' success in African arid zones may depend, however, on employment of adaptive heterothermy, to conserve body water.

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## ESTRADIOL EFFECT ON THE ADRENAL CORTEX CITOMORPHOLOGY IN RATS ACCLIMATED TO DIFFERENT ENVIRONMENTAL TEMPERATURES

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Many lines of evidence have stressed that estradiol provokes changes on the adrenal cortex (Malendowicz & Jachimowicz, 1982; Gorzalka & Moe, 1994). The literature concerning hyperthermia and the effect of estradiol on the citological characteristics of the adrenal cortex is unclear. The aim of this study was to determine the effect of estradiol on the cytohistology of the adrenal cortex of testectomized (Wistar strain) rats, acclimated to room (18-22<sup>0</sup>C) and a hyperthermic (34-36<sup>0</sup>C) environment. The control animals were intact and testectomized rats from both ambient temperatures. The acclimation of the animals to the hyperthermic environment was performed continuously: 30 days in a warm chamber at 34-36<sup>0</sup>C and relative humidity of 35-45%. On the animals was carried out a bilateral testectomy. Estradiol (estradiol dipropionate - 3,17 β-dipropioniloxi-1,3,5<sup>10</sup> - estratriena, Galenika) was administrated intramuscularly, in doses of 1 mg/100 g body mass (volume 0.1ml). The treatment was during four days, and sacrifice of the rats was 24 hours after the last dose. The results show that the treatment with estradiol significantly increased the adrenal mass, independently of the previous thermal acclimation (p<0.001), in comparison to the control and testectomized rats. The presence of the lipids vacuoles in the corticocytes in the testectomized and estradiol treated rats was slowly expressed in the rats from room temperature despite warm acclimated rats. From the results obtained, it can be seen that in the testectomized and estradiol treated rats, the presence of the zona intermedia was significantly prominent. The hyperemia of the adrenal cortex (especially in the rats from high temperature) was increased. The disturbance and de-organization of the histoarchitecture, especially in some parts of the adrenal cortex, was evident. Mitosis of the spongiocytes was observed. These changes were more prominent in the animals acclimated to room temperature (18-22<sup>0</sup>C).

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## GLYCOGEN PHOSPHORYLASE ACTIVITY DURING ACCLIMATION TO HIGH ENVIRONMENT TEMPERATURE IN FED AND FASTED RATS

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The aim of this experiment was to analyse the correlation of hepatic glycogen phosphorylase activity ( $a+b$  and  $a$ ) with liver glycogen content and blood glucose level in fed and 4-days fasted rats, during the acclimation to hyperthermic environment. The experiments were performed on adult Wistar male rats. Fed animals were divided into 8 groups: 1, 4, 7, 14, 21, 30 and 60 days of acclimation respectively, and control group. Four days fasted animals were grouped in 7: 0+4, 3+4, 10+4, 17+4, 26+4 and 56+4 days of acclimation, respectively, and control group. Heat acclimation was obtained in a special heat-chamber with regulated temperature of  $35 \pm 1$  °C and air humidity of 20-30%. Control animals were kept at a room temperature of  $20 \pm 2$  °C. After ether narcosis, liver pieces were taken and frozen in liquid nitrogen. Blood was taken from vena cava posterior. In fed rats, there was significant increased in the glycogen phosphorylase  $a$  activity only in the beginning of acclimation period. Liver glycogens content was significant increased after two weeks till the end of acclimation period. The correlation coefficient depending on time of exposition was significant ( $r=0.927$ ). High environmental temperature caused significantly decreasing of blood glucose level during whole acclimation period, ( $r=-0.956$ ). There is negative correlation of changes in liver glycogen content with blood glucose level ( $r=-0.746$ ). In fasting condition, there were decreased activity of both forms of glycogen phosphorylase activity ( $r=-0.617$  for  $a+b$ ,  $r=-0.589$  for  $a$ ), and decreased liver glycogen content ( $r = -0.896$ ) during whole period of acclimation. There is positive correlation between glycogen phosphorylase activity and liver glycogen content ( $r=0.712$  for  $a+b$ ,  $r=0.680$  for  $a$ ). Blood glucose level is not changed in fasted groups during acclimation to high temperature.

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## AN ENVIRONMENTAL STRESS INDEX (ESI) AS A SUBSTITUTE FOR THE WET BULB GLOBE TEMPERATURE (WBGT)

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In 1957, Yaglou and Minard developed the WBGT as a thermal index calculated as follows:  $WBGT = 0.7T_w + 0.2T_g + 0.1T_a$  where:  $T_w$  = wet bulb temperature,  $T_g$  = black globe temperature, and  $T_a$  = ambient temperature. This index has been used extensively for evaluating environmental heat stress in the US Army and Navy, during sport activities, and for determining safety guidance for workers in different occupations. However, WBGT was found to be limited in evaluating heat stress mainly due to the inconvenience of measuring  $T_g$ . A new environmental stress index (ESI), based on  $T_a$ , relative humidity (RH), and solar radiation (SR) was developed as follows:  $ESI = 0.63T_a - 0.03RH + 0.002SR + 0.0054(T_a \cdot RH) - 0.073(0.1 + SR)^{-1}$ . The purpose of this study was to determine whether the ESI could be used as an alternative for WBGT. The ESI was applied to databases obtained from 3 different climatic conditions in Israel, and was compared to the WBGT. The correlation coefficients between the two indices were found to be high as follows:

Climate	R <sup>2</sup>	P	Measurements
Hot/wet	0.982	0.001	8,328
Hot/dry	0.981	0.001	8,426
Extremely hot/dry	0.985	0.001	8,795

These results strengthen the possibility of evaluating heat stress by ESI using the more common, fast response and accurate climatic measures (e.g.,  $T_a$ , RH) and for the first time including solar radiation as a variable in thermal stress assessment. However, more studies should be done for further validation.

Yaglou, C.P. & Minard, D. (1957) Control of heat casualties at military training centers. *Archives of Industrial Health*, 16, 302-305.

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## ASSESSMENT OF HEAT INTOLERANCE

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The heat tolerance test (HTT) suggested by Shapiro et al. is applied in the Israeli army (IDF) for every post-heat stroke or heat exhausted soldier, and whenever there is a suspicion of heat intolerance (HI). The HTT consists of exercise in a hot/dry climatic condition of 40°C, 40% relative humidity (RH). After 10-min rest, subjects perform a treadmill walking at a constant speed of 1.34m·sec<sup>-1</sup> at a 2% grade for 120 min; the physiological criteria for heat intolerance are rectal temperature ( $T_{re}$ )  $\geq$  38.5°C or heart rate (HR)  $\geq$  160bpm. The purpose of this study was to re-evaluate the test and consider broadening it. Nineteen post heat stroke male subjects participated in this study. 5-6 weeks after the collapse, they performed an HTT, and a week later, another test consisting of the same protocol but in comfort (20°C, 50% RH) climate conditions (CTT).  $T_{re}$  and HR were monitored every minute. Oxygen consumption ( $VO_2$ ) was measured after 50 and 100 min of exercise and sweat rate ( $m_{sw}$ ) was calculated from changes in body weight before and after the exercise, corrected for water intake and urine. The measured physiological variables ( $T_{re}$ , HR) were higher ( $P<0.05$ ) during HTT in comparison to CTT, and the CTT results were not predictive for individual's tolerance to heat. No significant differences were found in  $m_{sw}$  and  $VO_2$  between the heat tolerant (HT) and the HI groups or between the two climates.

Five subjects were categorized as HI with  $T_{re}$  of  $\geq$  38.5°C or HR  $\geq$  160bpm. Based on the physiological strain index (PSI) and the slope of these variables, another subject could be categorized as HI. Therefore, it is suggested that the criteria for HI during the HTT will be as follows:

$T_{re}$ (°C)	HR (bpm)	PSI (units)
$\geq 38.5$	$\geq 160$	$>7$

During HTT, the slope was significantly higher ( $P<0.05$ ) for both  $T_{re}$  and PSI in the HI group between the 60th-70th minutes of the HTT, and after the 50<sup>th</sup> min throughout the HTT only for PSI. Absolute values of  $T_{re}$  and HR, without accounting for the dynamics of changes, are limited in their ability to assess HI. It is suggested that PSI, which accounts for both the absolute value and the change during the exposure, is a more suitable index for the assessment of HTT.

In conclusion, CTT is not essential for the assessment of heat intolerance. Adding the PSI and its slope in the assessment of heat intolerance strengthens the criteria and assures also that the change in  $T_{re}$  and HR and their dynamics during the test will be included in the evaluation.

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## THE ROLE OF GLOBAL RADIATION MEASURED BY A LIGHT SENSOR ON HEAT

### STRESS ASSESSMENT

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The Wet Bulb Globe Temperature (WBGT), developed in 1957 by Yaglou and Minard and considered to be as the most common heat stress index, is in use by the US army and has also been adapted by the World Health Organization (WHO). The WBGT is calculated from ambient temperature ( $T_a$ ), wet bulb temperature ( $T_w$ ), and black globe temperature ( $T_g$ ). The  $T_g$  is usually measured by a thermometer surrounded by a 6" blackened sphere, and quantifies the global radiation component of the thermal load. However, measuring  $T_g$  is cumbersome in many circumstances for two main reasons. First,  $T_g$  measurement requires about 30 min for the instrument to reach equilibrium. Second, the blackened sphere is of a relatively big size (6"). Therefore, measuring  $T_g$  becomes inconvenient and simply not practical, especially in transient situations. The purpose of this study was to evaluate a new relatively small (5 mm) light sensor for measuring solar radiation for use in heat stress assessment. Global radiation was using from three instruments: black globe ( $T_g$ ), Pyranometer (P), and light (L) sensor, in Israel for 25 days, from 09:00 am until 17:00 pm during September – October. Analysis of the daily collected data from these three instruments revealed, in spite of the different units, the same pattern for P and L during each day, where  $T_g$  was slower in its response and lagged behind P and L in its values. Therefore, we constructed a new model, which converted and predicted the L data measured in mv for P values measured in  $W \cdot m^{-2}$  as follows:  $P = -13.81 + 0.619L - 0.00012278L^2; W \cdot m^{-2}$ . The analyzed data contained 771 measurements and the correlation coefficient between P and L were very high ( $R^2 = 0.933$ ,  $P < 0.001$ ). Therefore, we concluded that the L sensor has the potential to measure global radiation. However, more studies should be done for further validation. This conclusion is very encouraging since there are already existing micro-sensors for measuring  $T_a$  and relative humidity (RH) in use. In this study, we explored the possibility of developing a new heat stress index based only on fast response environmental micro-sensors (e.g.,  $T_a$ , RH, and L) that can be assembled into a small portable device.

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**RAPHE PALLIDUS NEURONS MEDIATE INCREASES IN BROWN ADIPOSE  
SYMPATHETIC OUTFLOW EVOKED BY COOLING PREOPTIC HYPOTHALAMUS**  
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Neurons in the medial preoptic area of the hypothalamus (POAH) play an important role in sensing alterations in body core temperature and initiating autonomic and behavioral responses to return body temperature to a set point level. Disinhibition of neurons in the rostral raphe pallidus (RPa) has recently been shown to produce large increases in sympathetic nerve activity to brown adipose tissue (BAT). To begin to elucidate the pathways mediating the increases in brown adipose thermogenesis initiated to compensate for a fall in body temperature, experiments were performed to determine if an increase in the activity of neurons in the RPa was required for the stimulation of BAT sympathetic nerve activity in response to cooling of the POAH with a water-perfused thermode in rats anesthetized with an intravenous administration of urethane (800 mg/kg) and chloralose (60 mg/kg). For recording of sympathetic activity from nerve branches entering the ventral surface of the interscapular BAT, rats were paralyzed with tubocurarine (intravenous, 1.2 mg/kg), pneumothoracotomized and artificially-ventilated with 100% O<sub>2</sub>. Maintenance of adequate anesthesia was confirmed by the absence of withdrawal reflexes to noxious foot pinch during short periods when paralysis had worn off as indicated by spontaneous diaphragmatic contractions. Microinjection (60 nl) of the GABA<sub>A</sub>-receptor agonist, muscimol (2 mM), to inhibit local neurons in RPa produced a prompt and complete reversal of the increases in amplitude and frequency of the bursts in the sympathetic nerve to interscapular BAT evoked by perfusion of a stereotactically-positioned POAH thermode with chilled water (4°C). Similarly, prior microinjection of muscimol into RPa prevented the increase in BAT sympathetic nerve activity normally seen upon cooling of the POAH. These data indicate that neurons in RPa are required for the excitation of the sympathetic outflow to BAT that normally increases BAT thermogenesis in response to a fall in body core temperature. Such thermogenic neurons in RPa may function as sympathetic premotor neurons providing the essential excitatory drive to sympathetic preganglionic neurons controlling BAT thermogenesis.

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## **COLD VASCULAR HUNTING REACTIONS OF THE TOE IN COLD AIR IN NON-ATHLETES AND JUDO PLAYERS**

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Twenty three male non-athletes university students and 15 male university judo players were selected as subjects. The subjects, clad only in shorts and under shirts, sat resting in a climatic chamber at 17-18°C for 30 min. Then, they inserted their both legs up to the knees into a cold air box at 5°C for 60 min. Skin temperature on the center of dorsal surface of the distal phalax of the left second toe was recorded continuously during periods of 10 min before cold exposure, cold exposure and recovery for 20 min. In estimating the cold digital hunting reaction, following characteristics of changes in skin temperature during cold exposure; the temperature of the first rise (TFR), the time for the first temperature rise (TTR) and the mean skin temperature(MST)were used. The mean values of the skin temperature for 50 to 60 min after cold exposure was used as the MST. Anthropometric measurements including measurements of the second left toe girth (STG) were performed. Cold vascular hunting reactions were observed in 14 judo players (93%) and 11 non-athletes (48%). Judo players showed higher mean values of skin temperature before cold exposure and TFR while those of TTR and MST were smaller in judo players than in non-athletes. These characteristics of cold vascular hunting reactions of the toe in judo players might be induced by physical training as well as cold acclimation. Positive correlation was found between MST and STG. Skin temperatures of short and thick toe are higher because amount of heat dissipation from skin surface is proportional to skin surface and amount heat production in toe is proportional to mass of toe. Positive correlation was found between percentage of the body fat and temperature before exposure to cold (TB) or MST. Negative correlation was found between TTR and TFR or MST. These characteristics of the toe in cold air are essentially the same as those of finger observed during exposure of finger to cold water or cold air.

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## EFFICIENCY OF THERMOREGULATION IN PRECOCIAL AVIAN SPECIES IN THE PRENATAL PERIOD

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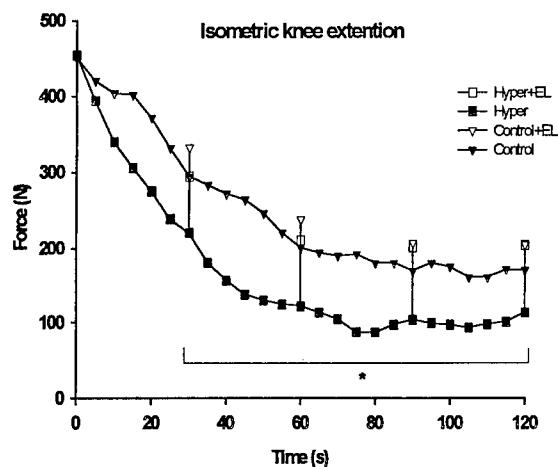
Precocial birds are able to increase thermoregulatory heat production (HP) immediately after hatching with decreasing ambient temperature (Ta). Information on HP during embryonic development in birds are contradictory, extending from a transient metabolic response to cooling with a  $Q_{10}$  of HP between 1.0 and 2.0 to a typical poikilothermic reaction in altricial bird embryos. Because of these differences standardised experiments for two precocial avian species (Muscovy duck, *Cairina moschata*; Domestic fowl, *Gallus gallus*) were carried out to search for evidence of endothermic reactions. The eggs were incubated at 37.5°C and at a relative air humidity of 70%. After 60 min the influence of lower (31.5°C, 34.5°C or higher (40.3°C) Ta on HP (oxygen consumption) and body core temperature (Taf) were estimated for a duration of 3 h. From the relationships between Taf and HP the  $Q_{10}$  of HP was calculated. The results of experiments show that (1) with decreasing Taf the HP dropped generally. In some cases, the parabola-like function describing these relationships showed extreme values situated 1 to 2.0°C lower than the maximum Taf. (2) The calculated  $Q_{10}$  crossed the 2.0 threshold mostly between 34 and 36°C Taf. In some cases no crossing was observed; mostly in older embryos or when the Ta was depressed quickly. (3) Generally, the efficiency of the endothermic reactions during the embryonic development was very low. During the last day of incubation, in the Muscovy duck as well as in the chicken after a 3-h-cold load with decreasing Ta the Taf dropped in a linear fashion with a regression coefficient about 1.10 in both species. (4) HP increases in embryos of both species during heat load was either less than calculated by the van't Hoff rule or HP dropped. Summarising, the results show that embryos of precocial birds are endothermic in the last third of incubation. The measured HP of endothermic animals at temperatures below the thermoneutral temperature is the result of two different processes: the thermoregulatory HP and the energy metabolism following the van't Hoff rule. In avian embryos a drop of Taf, mostly causes a decrease of net HP, but the decrease is more moderate than predicted by the van't Hoff rule. A  $Q_{10}$  of more than 2.0 demonstrates the absence of endothermy. A  $Q_{10}$  lower than 2.0 shows that an endothermic reaction occurs. When the  $Q_{10}$  is lower than 1.0 the increase of HP due to the thermoregulatory mechanisms is higher than the decrease of HP due to the van't Hoff rule and a net increase of HP occurs with decreasing core temperature. The goal of prenatal endothermy has to be different from that dealing with proximate support of thermoregulation. It is postulated that endothermic reactions during the prenatal period have ultimate influences rather than proximate influences on the efficiency of thermoregulation.

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## HYPERTHERMIA, EXERCISE AND CENTRAL FATIGUE IN HUMANS

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The mechanism(s) underlying hyperthermia-induced fatigue resulting from prolonged exercise in hot environments, is not well understood. Oxygen consumption, muscle blood flow and brief maximal voluntary contraction force (MVC) are similar in hyperthermic and normothermic athletes. Furthermore, neither the small increase in muscle glycogen breakdown, lactate production nor potassium release can explain the early fatigue with hyperthermia (Nielsen *et al.* 1993, Parkin *et al.* 1999). This study tested the hypothesis that "central fatigue" is a major factor associated with hyperthermia-induced fatigue. Seven endurance trained men [ $VO_{2\text{max}} 65 \pm 2 \text{ ml min}^{-1} \text{ kg}^{-1}$  (mean  $\pm$  SE)] exercised at 60%  $VO_{2\text{max}}$  on a cycle ergometer in a hot (40°C; 18% rh; hyperthermia) and in a thermoneutral environment (18°C; 48% rh; control). In the hyperthermic trial, the oesophageal temperature increased throughout the exercise period reaching a peak value of  $39.9 \pm 0.1^\circ\text{C}$  at exhaustion after 48  $\pm$  4 min of exercise. In the control trial, exercise was continued for 1 h without signs of fatigue with a stable core temperature of  $\sim 38.0 \pm 0.1^\circ\text{C}$ . Immediately after the cycle trials, subjects performed 2 min of sustained maximal isometric knee extension (MVC). During MVC electrical stimulation (250 ms square wave, EL) was delivered every 30 s to *n. femoralis*, in order to assess the degree of voluntary activation. **RESULTS:** MVC was similar during the first 5 s of contraction ( $454 \pm 38 \text{ N}$  in hyperthermia vs.  $450 \pm 48 \text{ N}$  in control). Hereafter the force declined in both trials, but the reduction in MVC was more pronounced in the hyperthermic trial, and significantly lower from 30 s to the end of the contraction in hyperthermia compared to control (see the Figure). Calculation of the voluntary activation percentage (MVC/MVC+EL) showed that voluntary activation was markedly lower in hyperthermia (54  $\pm$  7%) compared to control (82  $\pm$  6%). In contrast, total force of the knee extensors (MVC+ force from EL) was not different in the hyperthermic and control trial (see the Figure). **CONCLUSION:** These data demonstrate that hyperthermia results in a reduced force development during prolonged maximal isometric contractions, and the attenuated performance is associated with a "central fatigue" - i.e. reduced voluntary activation.



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## EFFECTS OF HYPEROSMOLALITY ON BODY TEMPERATURE AND ARTERIAL PRESSURE REGULATIONS DURING EXERCISE IN THE HUMAN

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Hyperosmolality by dehydration has been reported to suppress cutaneous vasodilation and sweating in hyperthermia (Takamata et al., 1997). However, the physiological role of the suppression has not been elucidated yet. Recently, Nakajima et al. (1998) reported in awake and passively heated rats that mean arterial pressure (MAP) decreased with a rise in tail skin blood flow (SkBF) in a hypovolemic and isosmotic condition, whereas in a hypovolemic and hyperosmotic condition MAP remained unchanged with the suppression of tail skin vasodilation. They concluded that plasma hyperosmolality stimulates pressor responses in the hypovolemic condition that subsequently contribute to arterial pressure regulation during heat stress. Takamata et al. (1995) reported in resting and passively heated humans that the hyperosmolality-induced suppression of sweating was released by oropharyngeal reflexes by drinking such a small amount of water as altered neither blood volume nor plasma osmolality. However, they did not find any significant changes in SkBF and MAP after the drinking. However, during exercise in heat and also in the hypovolemic condition, where SkBF competes with muscle blood flow, drinking would release the hyperosmolality-induced suppression of cutaneous vasodilation as well as sweating, resulting in a fall in MAP due to increased total peripheral conductance. To examine the hypotheses, 6 male subjects underwent 4 hydration states; 1) normal plasma volume (PV) and isosmolality trial, 2) low PV (PV = -10%) and isosmolality trial, 3) normal PV and hyperosmolality (Posm = 10 mOsm) trial, and 4) low PV and hyperosmolality trial. The hydration states were attained in separate experimental days in each subject by prior administration of diuretics, intravenous hypertonic NaCl solution and/or 24-hr water restriction. After the treatments, subjects exercised with a cycle ergometer at 60% of maximal aerobic power for 50 min in a hot environment (atmospheric temperature of 30°C and relative humidity of 50%). After esophageal temperature, forearm SkBF (by venous occlusion plethysmography), and sweat rate (with humidity sensor placed on chest surface) reached a plateau by 15–20 min of exercise, subjects drank the small amount of water of 37°C (100ml). Immediately after the drinking, SkBF and sweat rate in the hyperosmolality trials increased by 5–10% above the base line, accompanied by the reduction in MAP by 5–10 mmHg. However, we did not find any significant changes in these variables after the drinking in the isosmolality trials. There were no significant reductions in plasma norepinephrine and vasopressin concentrations after the drinking in every trial. These results suggest that the hyperosmolality-induced suppression of cutaneous vasodilation contribute to arterial pressure regulation regardless of blood volume during exercise in a hot environment in humans. Moreover, the suppression may be caused by attenuated active vasodilator system but not by enhanced active vasoconstrictor system such as by increased sympathetic nervous activity and/or vasopressin release. Finally, the suppression may be released by drinking via oropharyngeal reflexes.

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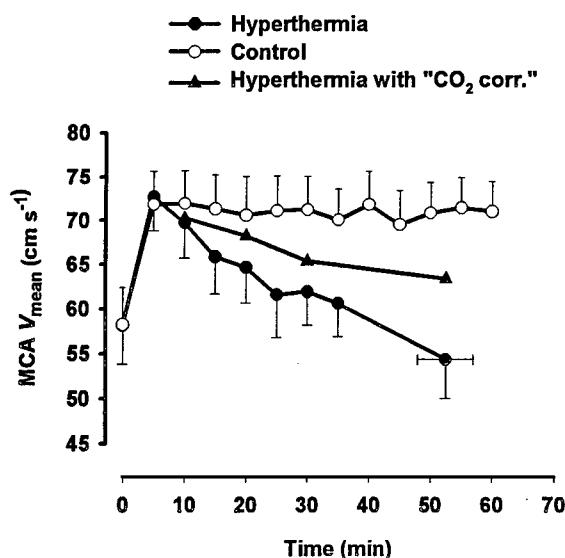
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## MIDDLE CEREBRAL ARTERY BLOOD FLOW VELOCITY IS REDUCED WITH HYPERTERMIA DURING PROLONGED EXERCISE IN HUMANS

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The present study examined the effect of hyperthermia on the middle cerebral artery mean blood velocity (MCA  $V_{mean}$ ) during prolonged exercise. We hypothesized that the cerebral circulation would be impaired when hyperthermia is superimposed during exercise and assumed that this could be observed as a reduced MCA  $V_{mean}$ . Eight endurance trained men [ $V_{O2max}$   $70\pm1$  ml min $^{-1}$  kg $^{-1}$  (mean  $\pm$  SE)] performed two exercise trials at 57% of  $V_{O2max}$  on a cycle ergometer in a hot (40°C; hyperthermic trial) and in a thermoneutral environment (18°C; control trial). In the hyperthermic trial, the oesophageal temperature increased throughout the exercise period reaching a peak value of  $40.0\pm0.1$ °C at exhaustion after 53±4 min of exercise. In the control trial, exercise was maintained for 1 h without any signs of fatigue and with core temperature stabilized at  $37.8\pm0.1$ °C after ~15 min of exercise. Concomitant with the development of hyperthermia, MCA  $V_{mean}$  declined by 26±3% from  $73\pm4$  cm s $^{-1}$  at the beginning of exercise to  $54\pm4$  cm s $^{-1}$  at exhaustion ( $P<0.001$ ). In contrast, MCA  $V_{mean}$  remained unchanged at  $70-72$  cm s $^{-1}$  throughout the 1 h control trial (see the figure). When individually determined regression lines for MCA  $V_{mean}$  and arterial  $P_{CO_2}$  obtained during preliminary exercise tests were used to ascribe for the differences in arterial  $P_{CO_2}$  between the hyperthermic and control trial, it appeared that more than half of the reduction in MCA  $V_{mean}$  (56±8%; see the figure) was related to a hyperventilation-induced drop in arterial carbon dioxide pressure. Declining cardiac output and arterial blood pressure during the hyperthermic trial presumably accounted for the last part of the reduction in MCA  $V_{mean}$ . The present results clearly demonstrate that the development of hyperthermia during prolonged exercise is associated with a marked reduction in middle cerebral artery mean blood velocity.



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## SWEATING REGULATION DURING EXERCISE WITH ALTERED METABOLIC HEAT PRODUCTION BY COMBINING DIET-INDUCED THERMOGENESIS

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It was reported that sweat rate depends on the total heat production during exercise rather than body temperatures (Nielsen, B., 1966). This observation is considered to be one of the bases for the hypothesis which the sweating activity is augmented by the non-thermal factor during exercise. In order to confirm this hypothesis, this study was directed to probe relationships between sweating activity, body temperature, metabolic heat production and workload during exercise with altering metabolic heat production by combining with diet induced thermogenesis (DIT). Experiments were carried out in three conditions on three different days in a climatic chamber set at 30 °C with relative humidity of 40 %. The five young male volunteers participated in the sequential experiments as follows. In the first experimental day (Condition E), the subjects rested in a sitting position for more than 50 min without food intake and then moved onto a bicycle ergometer placed on a bed balance and exercised at the workload of 50 W for 50 min. In the second experimental day (Condition E+D), the subjects ingested an 800 kcal meal 90 min before commencing with the exercise session at the workload of 50 W. In the third experimental day (Condition E-D), the workload was adjusted so that the metabolic heat production during exercise was offset by the diet by monitoring the oxygen consumption (Vo<sub>2</sub>) minute by minute using respipromonitor (AE280, Minato, Japan). The whole body sweat rate was recorded as a rate of body weight loss by using bed balance. Local sweat rate was measured on a flexor area of bilateral forearms according to capacitance hygrometry. The temperatures of esophageal (T<sub>es</sub>), tympanic (T<sub>ty</sub>), and skin surface (T<sub>s</sub>: chest, arm, thigh and calf) were continuously recorded by thermistors. T<sub>es</sub>, T<sub>ty</sub>, Vo<sub>2</sub> and HR were greater in Conditions E+D and E-D than in Condition E in the resting period immediately prior to exercise. After the onset of exercise, the degree of the increase in Vo<sub>2</sub> was greater in Condition E+D than in Condition E. In Condition E-D, the workload decreased on average to 35.8 W. The degree of increase in T<sub>es</sub>, T<sub>ty</sub> and mean body temperature calculated from T<sub>es</sub> or T<sub>ty</sub> and T<sub>s</sub> from the baseline of the resting period (without DIT) was greater in Condition E+D than in Condition E. On the other hand, the degree of increase in body weight loss and forearm sweat rate in Condition E+D corresponded with those in Condition E. However those sweat rates decreased in Condition E-D as compared with those in the other Conditions. The sweat rate correlated closer to the workload rather than the body temperature or metabolic heat production. These results reinforced the hypothesis that non-thermal mechanism facilitates the sweating activity during exercise.

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## MENTHOL-INDUCED EXCITATION IN CULTURED COLD-SENSITIVE NEURONS

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When applied to the oral cavity or skin, menthol elicits afferent impulses in cold fibers, and induces coolness or sensation of freshness. However, because it is difficult to access nerve endings, actions of menthol have not been clarified. In this study we analysed effects of menthol on cultured dorsal root ganglion (DRG) cells containing cell bodies of nerve fibers with measurements of cytosolic free  $\text{Ca}^{2+}$  ion concentration ( $[\text{Ca}^{2+}]_i$ ) and patch-clamp techniques. Wistar rats (2-14 days old) were anesthetized by diethyl ether and decapitated to isolate DRG. After dissociation with collagenase and trypsin, DRG cells were plated on a coverslip and cultured in DMEM containing 10 % fetal bovine serum. Menthol (l-menthol) dissolved in Krebs solution was bath-applied. For cold stimulation, temperature was lowered from room temperature(25-29 °C) by 10-15 °C. Temperature was monitored with a thermocouple close to cells. Before experiments, cells were loaded with Fura-2/AM (5 mM).  $[\text{Ca}^{2+}]_i$  was measured with Fura-2 microfluorimetry (ARGUS/HiSCA; Hamamatsu). Patch-clamp recordings were performed with EPC-7 (List). Data were acquired with MacLab (AD Instruments). Cooling induced an increase in  $[\text{Ca}^{2+}]_i$  in 10 % of DRG neurons. We identified them as cold-sensitive neurons. Menthol induced  $[\text{Ca}^{2+}]_i$  response in most (98 %) of the cold-sensitive neurons. The number of the menthol-sensitive neurons without cold-sensitivity was small. Menthol induced the  $[\text{Ca}^{2+}]_i$  increase in a dose-dependent manner, with an  $\text{EC}_{50}$  of  $37.9 \pm 7.58 \mu\text{M}$  ( $n=8$ ). When extracellular  $\text{Ca}^{2+}$  was removed, menthol did not induce the  $[\text{Ca}^{2+}]_i$  increase, indicating that menthol induced calcium influx. In whole-cell current-clamp recordings, menthol induced depolarization (receptor potential) leading to impulses. In voltage-clamp recordings (-60 mV), menthol induced inward currents, underlying the receptor potentials. Reversal potentials of the menthol-induced current suggested that menthol activated non-selective cation channels. We conclude that menthol induces depolarization and impulses through activation of non-selective cation channels in most of the cold-sensitive neurons.

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## THE COMBINED EFFECT OF REPETITIVE WORK AND COLD ON MUSCLE STRAIN AND FATIGUE

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Musculo-skeletal disorders cause considerable human suffering and financial losses. In epidemiological studies, both repetitive work and cold have been identified to be risk factors in the development of musculo-skeletal disorders. One reason to consider them as risk factors is that they can increase the strain of the working muscles and cause early fatigue. When exposure to those factors is frequently repeated, it may lead to overuse injuries and eventually musculo-skeletal disorders. To our knowledge, there is no information in the literature on the combined effect of low-intensity repetitive work and cold on muscle strain and fatigue. If they are additive, they may be a source of increased health risk. Thus, the purpose of this study was to evaluate and compare the amount of strain and fatigue caused by repetitive work in thermoneutral condition and repetitive work in cold condition. Eight healthy men volunteered as test subjects for the study. They were exposed once to 25°C (thermoneutral control) and 5°C. During the exposures the subjects performed six 20-minute work bouts, doing 10 % maximal voluntary contraction (MVC) wrist flexion-extension repetitive work. During the work bouts the electromyogram activity from the wrist flexors was measured (indicating the strain of the muscles). In addition, their maximal wrist flexion force was measured (indicating muscle fatigue) every 20th minute. The results show that during repetitive work in cold conditions the strain of the working muscles is approximately 20 % higher in comparison to work in thermoneutral conditions. In both conditions the forearm flexor muscles got fatigued. However, in cold condition the fatigue was almost twofold as compared to thermoneutral condition. In conclusion, when compared to thermoneutral condition, repetitive work in cold induces higher strain and higher rate of fatigue and in the long run may be considered as an increased risk for overuse injuries and musculoskeletal disorders.

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## EFFERENT POLYSYNAPTIC PATHWAYS FROM THE CNS TO THERMOREGULATORY END POINTS

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Brown adipose tissue (BAT) is a primary site contributing to thermal homeostasis through non shivering thermogenesis. It also plays a related and equally important role in diet-induced thermogenesis, dispersing excess energy and, in concert with food intake, regulating body weight. The central neural circuitry involved in the modulation of the activity of BAT via the sympathetic nervous system is relatively poorly defined. Detailed descriptions of these pathways has been limited by an inability of researchers to assign a "BAT- directed" tag to neurons deep within the CNS which are removed from their physiological endpoint by several synapses. The utilisation of neurotropic viruses which are transported retrogradely through chains of synaptically-connected neurons offers a solution to this problem. To this end, the Bartha strain of pseudorabies virus (PRV) has been used in the present experiments to map polysynaptic projections to the BAT in rats and, in conjunction with the immunostaining of candidate neuropeptides, these pathways (particularly in the hypothalamus) have been characterised in regard to their chemical phenotype. Sprague Dawley rats were anaesthetised with sodium pentobarbitone (60mg /kg ip) and PRV was injected into multiple sites in the interscapular brown fat. Rats were allowed to survive for varying periods to allow the virus to travel to different extents throughout the CNS. Rats were then re anaesthetised and perfused transcardially with 4% paraformaldehyde. Forty  $\mu$ m sections were cut throughout the brain, spinal cord and stellate ganglia. Both virus and a range of peptides were localised using appropriate antibodies and standard immunohistochemical techniques. The extent of double labelling of immunopositive profiles was assessed using fluorescence microscopy. Forty eight hours after inoculation of the BAT, virally-infected neurons were detected in the stellate ganglion and by 72 hours neurons infected with the virus were present in the ipsilateral thoracic spinal cord, but also in a range of medullary, pontine and hypothalamic sites considered "premotor" to sympathetic preganglionic neurons. These included the rostroventrolateral medulla, parapyramidal area, raphe pallidus and obscurus, A5 region, locus coeruleus, subcoeruleus, and peri aqueductal gray. The chemical signature of infected neurons in the stellate ganglia was consistent with recruitment of virus into fibres innervating adipocytes rather than blood vessels. In the hypothalamus, about 15% of neurons in the paraventricular nucleus contained oxytocin but did not express corticotropin releasing factor (CRF), galanin, vasopressin, cocaine amphetamine regulated transcript (CART) or melanin concentrating hormone (MCH). In the lateral hypothalamus however, MCH, CART and two members of the orexin family, orexin A and orexin B were abundantly coexpressed. Small numbers of infected neurons were found within the arcuate nucleus at the longest time interval studied and these contained leptin receptors and POMC. In the retrochiasmatic nucleus, by far the most prominent co-localisation occurred with CART accounting for approximately 85% of the neurons directed polysynaptically to the BAT. Orexin B and MCH are best recognised for their impact on feeding behavior and have been proposed as major mediators of this behavior via the lateral hypothalamus. Therefore the present data highlights an anatomical framework which may subserve thermogenesis but also indicates that regions, particularly in the lateral hypothalamus, known for their involvement in feeding may also contribute to thermogenesis. An intriguing possibility is that single neurons may coordinate both functions.

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## INDIVIDUAL DIFFERENCES IN BODY TEMPERATURE AND THE RELATION TO ENERGY EXPENDITURE: THE INFLUENCE OF MILD COLD

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Resting metabolic rate (RMR) adjusted for fat free mass (FFM) is subject to inter-individual variation. These differences in metabolic rate may be genetically determined and can have important health implications. Short-term exposure to cold is known to increase energy expenditure. This increase may also be specific for individuals. Moreover, it is not known which components of energy expenditure are involved and whether or not non-shivering thermogenesis contributes to the process.

Studies in animals and humans have shown that the differences in metabolic rate are related to differences in body temperature. However there is a controversy in results on the separate components of 24h energy expenditure (e.g. RMR, dietary induced thermogenesis, activity induced energy expenditure) and whether or not non-shivering thermogenesis contributes to the process.

The aim of this study was to determine the magnitude of inter-individual and gender differences in body temperature and RMR, during comfortable temperature and mild cold. The second goal was to study the relation between body temperature (BT) and RMR and the change of BT and RMR in reaction to a decrease in ambient temperature.

During the overnight stay at 22°C, sleeping metabolic rate (SMR) and intestinal temperature were measured. In the morning, RMR, intestinal, rectal and skin temperatures were measured for one hour at 22°C followed by three hours at 16°C. This experiment was conducted under standardised circumstances using a respiration chamber. Body composition was determined by underwaterweighing. Energy expenditure was corrected for body composition by calculation of residuals of the relation of energy expenditure versus fat free mass and fat mass.

Residuals of SMR and RMR were significantly related ( $p<0.001$ ,  $r^2=0.57$ ). It appears that individual levels of energy expenditure during the night remained during the day. We found a 5 % increase in RMR without an increase in electromyographic activity in response to a decrease in ambient temperature ( $p<0.05$ ), indicating non-shivering thermogenesis.

Core and rectal temperatures were higher in women than in men ( $p<0.01$ ) at both ambient temperatures. In spite of gender differences in skin temperature on specific sites, the average of proximal or distal skin temperatures was not significantly different and neither was average skin temperature. Temperature distribution in response to a decrease in ambient temperature was different between genders ( $p<0.05$ ).

In search for a relation between heat production and heat loss, RMR was compared with body surface area (BSA) and the temperature gradient between skin and ambient temperature. Stepwise regression with RMR as dependent variable and BSA and the gradient between skin and ambient temperature as independent variables, showed a significant contribution of the temperature gradient in addition to BSA at 22°C and the last hour at 16°C (respectively  $r^2 = 0.84$ ,  $r^2 = 0.70$ ,  $p < 0.001$ ). This shows that the gradient between skin and ambient temperature plays a role in the relation between heat production and heat loss.

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## EFFECTS OF THE CAPSAICIN ANALOGUE RESINIFERATOXIN ON THERMO-REGULATION IN ANESTHETIZED RATS

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Systemic administration of resiniferatoxin (RTX) or capsaicin, both of which share a homovanillyl moiety as a structural motif essential for bioactivity and thus are called vanilloids, is known to induce marked hypothermia in mammals. The vanilloid-induced hypothermia results from coordinated heat loss responses such as cutaneous vasodilation, sweating, and panting. In the present study, we studied the effects of RTX (50 µg/kg, s.c.) on heat production and heat loss simultaneously in rats. Adult male Wistar rats were anesthetized with urethan (1.1 g/kg, i.p.) and placed on a heating pad to maintain their baseline body temperature at ~36 °C. Administration of RTX induced triphasic changes in O<sub>2</sub> consumption (VO<sub>2</sub>): an immediate facilitatory phase with a peak at 50 min, an inhibitory phase with a minimal value at 100 min, and a long-lasting facilitatory phase. The temperature of skin (T<sub>s</sub>) also increased immediately after the RTX injection, suggesting cutaneous vasodilation and an increase in heat loss. The temperature of colon (T<sub>c</sub>) decreased immediately after the RTX injection and subsequently increased above the baseline level. The biphasic change in T<sub>c</sub> can be explained by the sum of heat loss and heat production: the effect of heat loss predominated during the initial 2 h, and that of heat production emerged after the end of the heat loss. In capsaicin-desensitized rats, RTX did not facilitate but inhibited VO<sub>2</sub> to a minimal value at 140 min. T<sub>s</sub> and T<sub>c</sub> did not change in these rats. Accordingly, the RTX-induced thermal responses were largely mediated by capsaicin (vanilloid) receptors, and the inhibition of VO<sub>2</sub> might be caused by a cell-nonselective action of RTX. However, pretreatment with the VN<sub>2</sub> vanilloid receptor antagonist ruthenium red (10 mg/kg, s.c.) enhanced the RTX-induced increase in VO<sub>2</sub>, suggesting attenuation of the inhibitory phase. Thus, the VN<sub>2</sub> receptors may mediate the inhibitory phase of VO<sub>2</sub> and receptors other than VN<sub>2</sub> may mediate the facilitatory phases of VO<sub>2</sub>. Ruthenium red also blocked the RTX-induced increase in T<sub>s</sub> and decrease in T<sub>c</sub>. Therefore, we consider that activation of the VN<sub>2</sub> receptors contributed to the hypothermia by inhibiting thermogenesis and facilitating heat loss, coordinately. Moreover, the results also indicate that the thermogenic responses were not caused by hypothermia. Pretreatment with the VN<sub>1</sub> antagonist capsazepine (10 mg/kg, s.c.), which reportedly reverses 1-mg/kg capsaicin-induced inhibition of thermogenesis in brown adipose tissue, did not affect the RTX-induced responses. Because RTX is 100-1000 times more potent than capsaicin, this amount of capsazepine might not have been sufficient to affect the RTX-induced responses. Accordingly, we could not determine the receptor subtype that mediates the RTX-induced thermogenesis. In rats with adrenal demedullation, the RTX-induced immediate facilitation of VO<sub>2</sub> was significantly attenuated but the long-lasting thermogenic phase remained. On the other hand, administration of the β-blocker propranolol largely attenuated both the immediate and long-lasting phases of RTX-induced thermogenesis. Therefore, the RTX-induced immediate thermogenesis was mediated by catecholamines released from the adrenal medulla; and the long-lasting thermogenesis, by sympathetic nerve activity.

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## THE EFFECTS OF HEAD AND NECK COOLING ON THERMOREGULATION, PACE SELECTION, AND PERFORMANCE

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The head and neck comprise only ~10% of total body surface area but have various physical and physiological properties favouring high heat transfer. Thus, cooling the head prior to or during exercise may be an efficient and effective means of reducing heat strain, as has been observed during mild exercise in the heat. Attenuating rises in brain or head skin temperatures might reduce discomfort and facilitate higher exercise intensities and body temperatures. However, strong cold-fferent supply from cutaneous thermoreceptors and/or a decrease in hypothalamic temperature due to selective cooling of the head could also provide false representation of the body's true thermal status and result in inappropriate physiological and behavioural thermoregulatory responses. This would accelerate heat storage and possibly lead to heat injury. The purpose of this study was to determine the physiological, psychophysical and performance-related effects of head and neck cooling during rest and exercise in a hot environment. Fourteen male distance runners (mean  $\pm$  SD;  $\dot{V}O_{2\text{max}}$ ,  $62 \pm 5 \text{ mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ; mass,  $76 \pm 6 \text{ kg}$ ;  $A_D$ ,  $2.0 \pm 0.1 \text{ m}^2$ ; age,  $24 \pm 4 \text{ y}$ ) participated as voluntary subjects. After two full familiarisation sessions, each subject completed four testing sessions (one per week) in an environmental chamber ( $33^\circ\text{C}$  and 55% rh), in balanced order. Each session consisted of 60-min seated rest followed by 30-min running at  $\sim 60\%$   $\dot{V}O_{2\text{max}}$  and then 15-min self-paced running to achieve maximum possible distance (without performance cues). The four sessions were identical except for the application and timing of head cooling: (1) No cooling during rest or exercise (control); (2) No cooling during rest but cooling throughout exercise; (3) Cooling throughout rest but not during exercise; and (4) Cooling throughout rest and exercise. The head was cooled using a water-perfused hood ( $1.1 \text{ L}\cdot\text{min}^{-1}$ ,  $1^\circ\text{C}$  inlet temperature) containing 6.3-m PVC tubing. Body temperature was measured from the core ( $T_c$  = rectal+oesophageal/2) and skin (9 sites), while sweat rate was determined by mass loss. Heat gain by the cap during rest (143 W) approximated the metabolic heat production ( $143 \pm 14 \text{ W}$ , from indirect calorimetry). It increased (ie.  $P < 0.05$ ) during exercise, becoming higher in exercise-only cooling (178 W) than in rest+ exercise cooling (157 W,  $P < 0.05$ ), but represented lower proportions of metabolic heat production (16 and 14%, respectively). Seated rest without head cooling led to increased  $T_c$  ( $0.10$ - $0.15^\circ\text{C}$ ) and heart rate ( $5 \pm 1 \text{ b}\cdot\text{min}^{-1}$ ), such that exercise began at lower  $T_c$  (by  $0.15$ - $0.20^\circ\text{C}$ ) and heart rate (by  $5$ - $8 \text{ b}\cdot\text{min}^{-1}$ ) in the precooled compared with uncooled conditions. At the end of exercise,  $T_c$  was higher in control than in all three head-cooling conditions (by  $0.20$ - $0.25^\circ\text{C}$ ), but heart rate was equivalent between conditions ( $173 \pm 11 \text{ b}\cdot\text{min}^{-1}$ ). Head cooling led to lower perceived temperature and improved thermal comfort of both the head and body during rest, except that the improvement in head comfort was not significant ( $P = 0.06$ ). All cooling conditions improved head comfort at the end of exercise, relative to control, but body comfort and perceived head temperature were only improved when cooling was applied during exercise. Perceived exertion increased during each exercise period and was equivalent between conditions. Sweat rate was lower during rest in the head cooling conditions (by  $0.06 \pm 0.06 \text{ L}\cdot\text{hr}^{-1}$ ). The 15-min run distance was higher with full-time cooling than with no cooling ( $3.3 \pm 3.4\%$ ) or precooling only ( $2.5 \pm 3.0\%$ ), and showed a similar trend against exercise-only cooling ( $2.3 \pm 2.9\%$ ,  $P = 0.08$ ). Despite a limited surface area, cooling the head reduced heat-related strain (core temperature, heart rate and sweat rate) during rest. This partially attenuated physiological ( $T_c$ ) and psychophysical (head comfort) strain during subsequent exercise, but did not improve performance (over 15-min, or  $\sim 4000 \text{ m}$ ). Head cooling before and during exercise reduced actual and perceived thermal strain and improved performance.

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## **THERMOREGULATORY RESPONSE TO HYPOXIA AFTER INHIBITION OF THE CENTRAL HEME OXYGENASE-CARBON MONOXIDE PATHWAY**

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A regulated decrease in body core temperature (T<sub>c</sub>), called anapyrexis, has been described to occur in a wide variety of species and seems to be an important adaptive response, but little is known about the mechanisms involved. Recently, carbon monoxide (CO) has been shown to be involved in thermoregulation and fever, but no report exists about its role in hypoxia-induced anapyrexis. Endogenous CO arises from the catabolism of heme to biliverdine, free iron and carbon monoxide (CO), a process catalyzed by the enzyme heme oxygenase (HO). Since it has been reported that HO is overexpressed during hypoxia, the present study was designed to test the hypothesis that the central HO-CO pathway plays a role in hypoxia-induced anapyrexis. To this end, we used intracerebroventricular (i.c.v.) injection of the HO inhibitor zinc deuteroporphyrin 2,4-bis glycol (ZnDPBG; 200 nmol). T<sub>c</sub> was determined in awake, unrestrained rats under each of the following three experimental conditions: 1. hypoxia (7% inspired O<sub>2</sub>) only; 2. i.c.v. ZnDPBG or its vehicle administered to rats kept under normoxia; 3. i.c.v. ZnDPBG or its vehicle administered to rats exposed to hypoxia. I.c.v. pretreatment with ZnDPBG or its vehicle did not alter T<sub>c</sub> during normoxia, confirming our previous observations that the central HO-CO pathway plays no tonic role in the maintenance of basal T<sub>c</sub>. However, i.c.v. ZnDPBG exacerbated the anapirexia evoked by hypoxia. These data imply that the central HO-CO pathway is an important modulator of hypoxia-induced anapyrexis in rats with a key function in the prevention of excessive decreases in T<sub>c</sub>.

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## CALF DERMAL BLOOD CONTENT AND SKIN TEMPERATURE DURING INCREMENTAL UPPER BODY EXERCISE

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During prolonged upper body exercise in cool conditions a gradual decrease in calf skin temperature has been observed, presumably due to redistribution of blood from the relatively inactive lower limb to the active upper body (Price & Campbell, 1997). However, little data exists regarding the relationship between leg blood flow and skin temperature during upper body exercise. Therefore, the aim of this study was to examine this relationship. Eight male subjects (mean  $\pm$  SD age,  $23.1 \pm 4.1$  yrs; height,  $179.3 \pm 9.4$  cm and weight,  $78.1 \pm 9.7$  kg) undertook incremental arm crank ergometry on an electronically braked ergometer (Lode, Groningen, the Netherlands). Subjects exercised for four minutes at workloads of 30, 50, 70 and 90W at a cadence of 70 rev. $\cdot$ min $^{-1}$  with 6 minutes rest between stages. Following the last rest period subjects exercised continuously at 20W.2min $^{-1}$  from an initial load of 110W until volitional exhaustion. Environmental temperature was similar for all trials ( $21.3 \pm 1.3$  °C). Expired air was analysed by an online gas analysis system (Vacumed, Turbofit, USA). Calf dermal blood content was measured by a photoplethysmograph (Rheo Dopplex II, Huntleigh Diagnostics, UK) attached 10 cm superior to the medial malleolus. Calf dermal blood content (CDBC) and refill times were assessed via standard photoplethysmographical techniques (post 10 dorsiflexions in the seated position). Skin temperatures were measured via a Grant meter logger (Squirrel 1200 Series, UK) from thermistors attached to the forehead, forearm, upperarm, back, chest, abdomen, thigh and calf (medial and lateral). Aural temperature was measured from a thermistor inserted into the auditory canal and insulated with cotton wool. All temperature measures were recorded at one minute intervals. Blood flow was recorded immediately after the cessation of each exercise stage and at volitional exhaustion. All data were analysed by repeated measures Analysis of Variance. During incremental exercise CDBC decreased to  $86.0 \pm 16.0$ ,  $79.7 \pm 7.0$ ,  $83.2 \pm 12.6$ ,  $76.4 \pm 10.7$  and  $57.5 \pm 12.6$  % of initial values at 30, 50, 70, 70W and volitional exhaustion, respectively ( $P < 0.05$ ). Lateral calf skin temperature decreased from  $29.8 \pm 0.7$  °C at rest to  $29.7 \pm 0.6$ ,  $29.5 \pm 0.6$ ,  $29.3 \pm 0.5$ ,  $29.0 \pm 0.5$  and  $28.2 \pm 0.4$  °C at 30, 50, 70, 70W and volitional exhaustion, respectively, whereas upper body skin temperatures increased ( $P < 0.05$ ). CDBC and lateral calf skin temperature decreased linearly with exercise intensity ( $P < 0.05$ ;  $R^2 = 0.935$ ;  $P < 0.05$ ;  $R^2 = 0.996$ , respectively). The relationship between CDBC and lateral calf temperature was also linear ( $R^2 = 0.865$ ). No differences were observed between medial and lateral calf skin temperatures. The results of this study suggest that calf dermal blood content decreases with increases in exercise intensity and may represent a similar graded response akin to that observed for visceral blood flow during lower body exercise. In addition, either lateral or medial calf skin temperature may be used as an indication of calf dermal blood content and haemodynamics during upper body exercise.

Price, M.J. & Campbell, I.G. (1997) Thermoregulatory response of paraplegic and able-bodied athletes at rest and during prolonged upper body exercise and passive recovery. *European Journal of Applied Physiology*, 76, 552-560.

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## THE EFFECT OF FORMULA USE ON MEAN SKIN TEMPERATURE ESTIMATES DURING PROLONGED AND INCREMENTAL UPPER BODY EXERCISE

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A range of formulae have been employed to estimate mean skin temperature (MST). Goss et al (1980) examined a range of MST formulae to determine the most appropriate estimate of MST during cycle exercise, however, no such comparison has been reported in the literature for upper body exercise. This is of particular importance in light of decreases in calf skin temperature ( $T_{calf}$ ) during prolonged upper body exercise in cool conditions (Price & Campbell, 1997). Consequently, the use of formulae incorporating such a parameter in their calculation may bias estimates of MST. Therefore, the aim of this study was to examine the effect of formula use on estimates of MST during upper body exercise. Subjects undertook either an incremental arm crank ergometry (ACE) protocol (Study 1;  $n=8$ , mean  $\pm SD$  age,  $23.1 \pm 4.1$  yrs; height,  $179.3 \pm 9.4$  cm and weight,  $78.1 \pm 9.7$  kg) or prolonged ACE at 60%  $VO_{2\text{peak}}$  in cool ( $21.5 \pm 1.3^\circ\text{C}$ ) and warm ( $31.3 \pm 0.4^\circ\text{C}$ ) conditions (Study 2;  $n=7$ ; age,  $29.0 \pm 4.5$  yrs; height,  $176.3 \pm 8.4$  cm and weight,  $64.2 \pm 11.8$  kg). The incremental exercise test involved four, four-minute workloads (30, 50, 70 and 90W) at a cadence of  $70 \text{ rev min}^{-1}$  and 6 minutes recovery between stages. After the fourth rest period subjects exercised continuously at  $20\text{W } 2\text{min}^{-1}$  from an initial load of 110W until volitional exhaustion. Skin temperatures were measured via a Grant meter logger (Squirrel 1200 Series, UK) from thermistors attached to the forehead, forearm, upperarm, back, chest, abdomen, thigh and calf. Aural temperature was measured from a thermistor inserted into the auditory canal and insulated with cotton wool. Data was recorded at rest, at the end of each exercise stage and volitional exhaustion in study 1 and every 5 minutes after resting measures during study 2. Estimates of mean skin temperature were obtained from the formulae of Nadel, Burton, Ayling, Ramanathan, Newburgh-Spealman and weighted and unweighted formulae of Goss et al. (1980) as outlined by Goss et al. (1980). All data were analysed by two-way repeated measures Analysis of Variance. Main effects were observed for workload/time and formulae ( $P < 0.05$ ) for both studies. No interactions were observed ( $P > 0.05$ ). Post hoc analysis revealed the formula of Burton ( $T_{calf}$  weighting 0.36) to estimate the lowest MST values in all trials whereas the formula of Ayling (no  $T_{calf}$  employed in calculation) produced the warmest estimates of MST. The differences between warmest and coolest estimates of MST increased over time during prolonged ACE in cool conditions ( $T_{calf}$  decreasing), was greatest during incremental exercise as workload increased ( $T_{calf}$  decreasing), but remained constant during prolonged ACE in warm conditions ( $T_{calf}$  increasing). The results of this study suggest that the formula choice biases MST estimates where calf temperature is involved in the MST calculation (or the weighting is large), exercise intensity increases or where cool conditions are employed.

Price, M.J. & Campbell, I.G. (1997) Thermoregulatory response of paraplegic and able-bodied athletes at rest and during prolonged upper body exercise and passive recovery. *European Journal of Applied Physiology*, 76, 552-560.

Goss, A., Herbert, W.G. & Kelso, T.B. (1980) A comparison of mean skin temperatures during prolonged cycle exercise. *Research Quarterly for Exercise and Sport*, 60, 292-296.

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## CHANGES IN SKIN TEMPERATURE IN THE HANDS AND FEET OF YOUNG AND ELDERLY SUBJECTS IN RESPONSE TO LOCAL COOLING

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An important component in the regulation of body temperature is skin blood flow, especially in peripheral sites such as hands and feet. Any impairment of vasomotor control in these skin areas can, in addition to causing tissue damage, compromise thermoregulation and may, under certain circumstances, be detrimental for health. While patho-physiological related changes in skin blood circulation (usually reduced blood flow) are often clearly discernible, natural age related changes in the healthy elderly are less well documented and opinions vary concerning the degree and pattern of these changes. The object of this study was to examine how peripheral circulation in the extremities (hands and feet) in young and elderly subjects is affected by a short period of local cold exposure. The experiments, which took place in a climatic chamber under thermoneutral ambient conditions ( $T_a$  26 - 28°C), were carried out in 12 young male (mean age 25 years) and 8 elderly female and 4 elderly male (mean age 77 years) healthy volunteer subjects. During the experiments, the lightly clothed subject sat in a comfortable stool while resting either their hands or their feet (palm/sole down) on a thin grid made of nylon netting. Following a 30 minute control period to establish base line values (a vasodilated state with particular emphasis on the presence of thermal symmetry between the left & right sides of the body) the right hand or the left foot was immersed for a period of 2 minutes in 10°C water (a thin plastic bag was worn during the immersion period to avoid skin wetting). Throughout the experiments measurements of surface temperatures (infra-red thermal imagery and thermocouples) and skin blood flow (laser Doppler flowmetry) were made at multiple skin sites (finger/toes and back of hand/foot). Blood pressure and heart rate were also measured. Calculations were made of the time taken for skin temperatures in the 'cold' hand or foot to regain 80% of the cold induced drop in temperature (recovery time). None of the subjects found the experiments to be discomforting. The main findings were:- 1) Under thermoneutral ambient conditions skin temperatures on the hands and feet were lower in the elderly than in the young subjects. 2). Under thermoneutral ambient conditions skin temperatures on the feet were always lower than on the hands in both the young and elderly subjects. 3) Recovery time after cooling was always longer in the elderly subjects, both for hands and for the feet. 4) In both young and elderly subjects recovery time was always shorter for the hands than for the feet. Rewarming of the hands and feet involves both active (e.g. arterio-venous anastomoses) and passive components. The results support previous findings which indicate that the active component of the re-warming mechanism is altered with increasing age although conclusions concerning the mechanisms involved cannot be made from this study

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## COLD PROBLEMS AND UPPER LIMB MUSCULAR STRAIN IN FOOD PROCESSING INDUSTRY

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Due to repetitive and monotonous manual work, cold environment, cold products, air movements and moisture, workers in the cooled facilities of food processing industry face many health and performance risks. Upper limb overuse symptoms are common reason for complaints and sick leaves. However, the role of cold in upper limb performance, physical strain, fatigue and overuse symptoms in food processing industry are not fully understood. Therefore, a questionnaire study was done in four companies of meat processing industry and one dairy. Personal characteristics of workers, their work history, work environment and experienced cold hazards as well as health problems were asked from 1490 workers. Moreover, during ca. 4 h sessions of sausage packing at 5 - 7 °C, skin temperatures (12 sites of upper limbs) and work load (assessed by electromyographic activity of *m. extensor digitorum* and *m. flexor carpi radialis*) were measured in female workers with (n = 6) and without (n = 6) upper limb musculoskeletal symptoms. The responses (n = 1117) to the questionnaire show that 51 % of the respondents worked at 0 - 5 °C and 34 % at 6 - 10 °C. Complaints of hand and finger (89 % of the respondents), wrist (58 %), toe (59 %) and shoulder (52 %) cooling were most common. Musculoskeletal pain was more frequent in cold environment in all parts of the body, especially in hands, arms and neck, when compared to work in Finnish food processing industry in warm facilities (Koskinen *et al.* 1997). In comparison to men, considerably higher percentage of women suffered cold problems during the early working years and the years did not increase the women's cold problems as it did in men. The measurements showed that workers with musculoskeletal symptoms had consistently lower ( $p < 0.05$ ) skin temperatures in shoulder (above *m. deltoideus*) area and after ca. 3 h work also in forearm (above *m. extensor digitorum*) and neck-shoulder (*m. trapezius*) areas. Muscular strain of forearm muscles was negatively correlated ( $p < 0.05$ ) with forearm skin temperatures. In conclusion, the results show that in food processing industry there are marked cold problems especially in the neck-shoulder area and in the hands and fingers, cooling significantly increases muscular strain of work and musculoskeletal symptoms seem to be associated with decreased shoulder and arm skin temperatures.

Koskinen, K., Olkinuora, P., Könni, U. & Kaleva, S. (1997) Work environment and workers' welfare in food processing industry (in Finnish). *Työ ja Ihminen*, 10, 91-97.

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## **THERMAL RESPONSES OF FIGHTER PILOTS DURING SIMULATED PARACHUTING IN THE COLD**

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Ejection from a fighter aircraft can expose the pilot to extreme cold and windy conditions. Depending on the type of aircraft the parachute opens at the altitude of 5000 or 3000 m. In these cases descending takes 8 to 13 min at the descend velocity of  $6 \text{ ms}^{-1}$ . The purpose of this study was to investigate the cooling rate of the body during simulated parachuting. Parachuting was simulated in a wind tunnel at air temperature of  $-35^\circ\text{C}$  and wind velocity of  $10 \text{ ms}^{-1}$ . Seven male pilots volunteered for the study as subjects. The subjects were hanging from the ceiling in their harness for 8 min. The subjects were facing the wind for the first 1 min and for the last 30 s of the total 8 min, otherwise back was against the wind. The subjects wore their personal F-18 winter aircrew garments. Breathing mask was kept on and both of the two visors were down. Flight gloves were used. The subjects were allowed behaviourally thermoregulate their hands. During the exposure skin temperatures were measured. Mean skin temperature, calculated as area weighted mean, was  $28.2 \pm 0.5^\circ\text{C}$  (mean  $\pm$  SE) at the end of the 8 min exposure. Cheek (bare) and chin (covered) temperatures were  $9.1 \pm 2.1^\circ\text{C}$  ( $3.2 - 13.8^\circ\text{C}$ ) and  $27.2 \pm 0.5^\circ\text{C}$  ( $25.8 - 27.0^\circ\text{C}$ ), respectively, at the end of the exposure. Finger temperature was  $6.0 \pm 1.2^\circ\text{C}$  ( $3.2 - 10.7^\circ\text{C}$ ). Risks of frostbites in cheek or fingers were apparent in some individuals. Thin flight gloves did not protect cooling of the fingers. Predicted time for frostbite (skin temperature of  $0^\circ\text{C}$ ) for cheek was 10 - 14 min and for fingers 15 - 18 min. In order to maintain performance and to avoid health hazards, more attention should be paid on developing better protection for hands and face.

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## VALIDATING FIELDABLE INDICES OF CORE TEMPERATURE

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Standard methods of core temperature ( $T_c$ ) measurement, in the oesophagus ( $T_{es}$ ) or rectum ( $T_{re}$ ), are poorly suited to athletic, occupational or military application, hence the desire for development of less obtrusive indices. Gastro-intestinal radio-pill ( $T_{gi}$ ), infra-red tympanic ( $T_{ty}$ ) and insulated skin ( $T_{inskin}$ ) temperatures may provide a solution but are not faultless. The measurement of  $T_{gi}$  is expensive and incurs problems with sequential application.  $T_{ty}$  is readily contaminated by ambient temperature if methodology is inadequate.  $T_{inskin}$  shows some promise as a surrogate index of  $T_c$  (Taylor, et al., 1998), but has not been fully validated. We examined the accuracy of  $T_{inskin}$  as a surrogate measure of  $T_c$  in military applications - including periods of rising, falling and static  $T_c$ , under various environmental conditions. Subjects were thirteen heat-acclimatised, euhydrated, healthy volunteers from the Australian Army (mean $\pm$ SD: age = 25 $\pm$ 5 y; height = 173 $\pm$ 11 cm; mass = 74 $\pm$ 12 kg). Following two familiarisation sessions, subjects participated in experimental sessions with various environmental conditions; Wet-Bulb Globe Temperature (WBGT) = 21.2°C (Dry Bulb (DB)=25°C), 25.9°C (DB=30°C), 29.7°C (DB=40°C) and/or 32.2°C (DB=35°C). Each session was conducted at least one week apart and consisted of 15-min seated rest (REST), 45-min treadmill walking (5-6 kph at 5-10% grad; WALK1), 15-min manual load handling (repeatedly lifting and carrying a 20-kg crate; LOAD), a second walk, of up to 60 min (5-7 kph at 0-10% grad; WALK2) and 20-min seated recovery (RECOV). Subjects wore standard army combat uniform and carried a 20-kg pack during walk phases.  $T_c$  was measured at 1-min intervals from  $T_{re}$ ,  $T_{es}$ ,  $T_{gi}$  and  $T_{inskin}$  (positioned over spine at T2-T4), and from  $T_{ty}$  at 15-min intervals.  $T_{inskin}$  showed a stronger association with  $T_{es}$  ( $r=0.68$ ,  $n=3424$ ,  $p<0.01$ ) than with  $T_{re}$  ( $r=0.64$ ,  $n=3957$ ,  $p<0.01$ ), independently of environmental condition. When separated by environmental condition the associations become stronger with increasing heat stress. For example, the relationship between  $T_{es}$  and  $T_{inskin}$  improved with greater heat stress (WBGT: 21.2°C,  $r=0.42$ ; 25.9°C,  $r=0.65$ ; 29.7°C,  $r=0.78$ ; 32.2°C,  $r=0.80$ ). When separated by exercise phase,  $T_{inskin}$  predicted  $T_c$  poorly during REST (eg.  $T_{es}$ : WBGT 32.2°C,  $r=0.04$ ,  $n=136$ ,  $p>0.05$ ,  $SEE=0.13$ ) and LOAD carriage (eg.  $T_{es}$ : WBGT 32.2°C,  $r=0.4$ ,  $n=113$ ,  $p<0.01$ ,  $SEE=0.37$ ), even under increased heat stress. However during WALK1, WALK2 and RECOV,  $T_{es}$  and  $T_{inskin}$  associations ranged from moderate to strong:  $r=0.67$ ,  $n=382$ ,  $p<0.01$ ;  $r=0.56$ ,  $n=107$ ,  $p<0.01$ ;  $r=0.86$ ,  $n=127$ ,  $p<0.01$ , respectively, depending on phase.  $T_{gi}$  had a stronger association with  $T_{re}$  ( $r=0.92$ ,  $n=3198$ ,  $p<0.01$ ;  $T_{re} = 0.922T_{gi} + 2.84$ ,  $SEE=0.25$ ) than with  $T_{es}$  ( $r=0.83$ ,  $n=2652$ ,  $p<0.01$ ;  $T_{es} = 0.746T_{gi} + 9.19$ ,  $SEE=0.34$ ), whereas  $T_{ty}$  tended to be a poorer predictor of both  $T_{re}$  ( $r=0.69$ ,  $n=334$ ,  $p<0.01$ ;  $T_{re} = 0.47T_{ty} + 20.0$ ,  $SEE=0.49$ ) and  $T_{es}$  ( $r=0.77$ ,  $n=310$ ,  $p<0.01$ ;  $T_{es} = 0.47T_{ty} + 19.5$ ,  $SEE=0.39$ ). In summary,  $T_{inskin}$  represented  $T_{es}$  with more confidence than  $T_{re}$ . The relationship between  $T_{inskin}$  and  $T_c$ s improved with increasing heat stress. Exercise phases where  $T_c$  remains relatively constant displayed an uncoupling of  $T_{inskin}$  and  $T_c$ s, whereas epochs with increasing or decreasing  $T_c$  produce moderate to strong  $T_c$  to  $T_{inskin}$  dependence.  $T_{gi}$  by radio-pill thermometry generally had a stronger association with standard measures of  $T_c$  than did  $T_{ty}$  by infra-red thermometry.

Taylor, N.A.S., Wilsmore, B.R., Amos, D., Takken, T. & Komen, T. (1998). Insulated skin temperatures: Indirect indices of human body-core temperature. DSTO-TR-0752. Melb.

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## AGE-DEPENDENT HEAT SHOCK RESPONSE OF A DIURNAL RODENT SPECIES FROM EXTREME DRY AND HOT ENVIRONMENTS

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Two unique characteristics, heat tolerance and longevity, make the golden spiny mouse (*Acomys russatus*), a diurnal rodent inhabiting extreme hot and dry habitats, a good research model for heat shock response in relation to aging. The aim of this study was to provide a critical testing to hypotheses currently based on cell culture and laboratory animal experiments. Young (5-8 month) and Old (3-5 years) mice were compared at the whole organism and the cellular levels. Mice were acclimated to an ambient temperature of 27°C under a 12L:12D photoperiod. Young mice (n=10) and old mice (n=8) were exposed to 44°C. Plasma cortisol concentration, HSF1 (heat shock factor 1) activation and HSP70 (72 and 73kd heat shock proteins) expression in the liver were measured in young (n=6) and old (n=6) mice exposed to 44°C for 30 and 90 minutes. Control mice (n=6) were tested without being exposed to heat. The animals were sacrificed and tissues were quickly removed. The old mice thermoregulatory capacity was lower than that of young mice, as mortality at 44°C started 30 minutes earlier than in young mice and reached 50% an hour earlier. No significant difference in plasma cortisol concentration was found between old and young mice. Lower HSF1 activation and HSP 70 expression was found in old mice compared to young ones. Unexpected expression of both HSP 72 and HSP 73 was found in old and young mice of both the control and exposure animal groups. These results support existing theories of aging and the molecular heat shock response. However, the ability of *A. russatus* to maintain its cortisol levels at an old age, and the constitutive expression of HSP 72kd (the inducible form), present an organism with unique cellular and systemic adaptation to diurnal activity in extreme hot and dry habitats.

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## FEVER AND HPA-AXIS ACTIVATION IN RESPONSE TO LOCALIZED PERIPHERAL INFLAMMATORY STIMULATION

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Fever and the activation of the hypothalamic-pituitary-adrenal (HPA) axis are characteristic brain controlled components of the acute-phase response which result, in most cases, from peripheral signals entering the central nervous system. In experimental animals the acute-phase response can be induced by systemic administration of bacterial lipopolysaccharide (LPS) which, in turn, causes a circulating cascade of proinflammatory cytokines. These cytokines, namely interleukin- (IL-) 1, IL-6 and tumor necrosis factor (TNF), are traditionally regarded as humoral factors which are involved in the induction or maintenance of brain controlled sickness signs including fever and HPA-axis activation. More recently a role of afferent fibers of the vagus nerve in transmission of inflammatory immune signals from the body periphery to the brain has been proposed since subdiaphragmatic vagotomy attenuates fever, sickness behavior and HPA-axis activation under certain experimental conditions. In this study we investigated whether also afferents from cutaneous nerves can act as a neural route for immune-to-brain communication. Male guinea pigs (*Cavia aperea porcellus*) were anesthetized with 100 mg/kg ketamine and 4 mg/kg xylazine and the following components were chronically implanted: biotelemetry transmitters for measurement of body temperature into the abdominal cavity; catheters for blood sampling into the carotid artery; cylindric teflon chambers, open at both sides and equipped with a catheter for drug injection or collection of lavage fluid, into a subcutaneous cavity. Both, injection of a high (100  $\mu$ g/kg) or a low (10  $\mu$ g/kg) dose of LPS into the subcutaneously implanted chambers induced fever. An activation of the HPA-axis as indicated by increased levels of circulating cortisol only occurred in response to the high LPS-dose. The febrile response to the low, but not to the high dose of LPS, was significantly attenuated but not completely abolished by administration of 10 mg/kg of the local anesthetic ropivacaine into the inflamed subcutaneous tissue area, a procedure which blocked the transmission of afferent neural signals from this area for 6-8 hours. HPA-axis activity was not altered by treatment with the local anesthetic. This finding indicated a participation of humoral and, in response to the low LPS dose, also neuronal signals in the induction of the brain controlled fever response. In order to investigate which humoral signals may derive from the local site of inflammation we measured circulating levels of LPS (*limulus amebocyte lysate endotoxin assay*) and proinflammatory cytokines (specific bioassays for TNF, IL-1 and IL-6) at distinct time intervals prior and after injection of LPS into the subcutaneous chamber. With the exception of one animal injected with the high LPS-dose, LPS was not detectable in plasma after its administration into the chamber. In response to LPS, proinflammatory cytokines were produced in high concentrations within the inflamed subcutaneous tissue area and could be measured in lavage fluid collected through the catheter of the implanted chamber. From these cytokines only IL-6 spilled over from the subcutaneous chamber area into the circulation in considerable amounts. In response to the low dose of LPS, IL-6 was the only cytokine which could be detected in plasma at all. In conclusion, IL-6 is a likely candidate to act as a humoral signal which participates in fever induction in this experimental model of a localized subcutaneous inflammation.

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## METABOLIC HEAT AND THERMAL COMFORT IN OFFICES

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Dissipation of excess metabolic heat is necessary for human thermal comfort. International standards ISO 7730 (1994) and ASHRAE Standard 55 (1992) are based on steady state equilibrium theories of heat exchange between the subject and the environment. They rely on evaluation or estimation of physical variables (air temperature, mean radiant temperature, air velocity and humidity) and personal variables (insulation provided by clothing and rate of production of metabolic heat). Despite a solid research base dissatisfaction with thermal comfort remains the most common cause of complaint by office workers. In recent years a number of careful field studies have been conducted in an effort to resolve this anomaly. In this work researchers find the most challenging task is the determination of metabolic rate of subjects. The four physical variables can be measured with high orders of accuracy. The sum of reported values for each item of clothing gives a reasonably accurate estimate of the total. In the absence of a practicable method of measuring metabolic rate directly in the field, participants indicate types of activity performed during the immediately preceding hour and a weighted pro rata total of values as tabulated in the ISO and ASHRAE standards is accepted as an estimate of the current rate. A study by Brager et al (1994) reviewed estimates of group average metabolic rate from several high quality field studies and concluded that an robust value for a large group of office workers is 1.2 met. The author has conducted a longitudinal field study of thermal comfort in an office building in Sydney, Australia. The site was visited on two occasions each month from July 1996 to June 1998 with a break of five months from February to August 1997. On each occasion participants were visited twice, in the morning and afternoon. A total of 1626 sets of data including details of metabolic activity over the preceding hour were obtained from 144 participants. Estimates of metabolic rate showed considerable between subject variation over a range from 1.0 to 1.9 met. Fifty percent were less than 1.2 met and 31 percent were above. 532 morning/afternoon pairs were collected and reveal that for 78 percent of respondents the estimate for the afternoon different from that obtained in the morning. Mean values were, however, constant at 1.2 met during the whole period of the study. ISO rules for estimation of comfort temperature indicate a change of 0.1 met will produce a change equivalent to a temperature change of 1 oC and a change of 0.4 met will cause a sensation change of at least 2.5 oC. It is concluded that the value of 1.2 met for a large group of office workers is robust; but that random individual variability caused by the changing demands of the job and possibly lunchtime recreation may be an unrecognised and difficult to diagnose cause of much of the complaint about thermal comfort in offices. The only corrective for this situation would be individual control of the personal thermal environment.

Brager, G.S., Fountain, M., Benton, C.C., Arens, E.A. & Bauman, F.S. (1994) A comparison of methods for assessing thermal sensation and acceptability in the field. *Thermal Comfort: Past Present and Future*, 17-38. BRE, London.

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## DIGESTION-RELATED THERMOGENESIS IN PIGEONS

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The pigeon stores ingested food in its crop during the day and digests during the night. Recently we have found that there is interaction at effector level between shivering and digestion-related thermogenesis. Digestion provides heat that replaces shivering to maintain body temperature at night (Rashotte et al. 1999). We suggested that a body temperature (T<sub>b</sub>) value for nocturnal plateau is set according to energy status to be read in certain time window of each daily cycle. Still open remained the question, whether pigeons are able to control the proper timing of digestion during the day and night, and whether digestion provides heat to be adjusted optimally according to thermoregulation and energy balance. We recorded telemetrically T<sub>b</sub> and locomotor activity of pigeons both at T<sub>a</sub> 22°C or 5°C under 12L:12D photoperiod. Mini-Mitter transmitters (Model VM-FH) were implanted under isoflurane anaesthesia, 5 % for induction and 1.5-2 % for maintenance. The pigeons were treated with buprenorphine postoperatively for 24 hours. Rate of digestion was estimated by recording continuously dropping mass accumulation on a load cell. Food was given in one-hour-pulse either two hours after lights on in the morning, or three hours before lights off in the evening. Total fresh and dry mass of excreta within a day was measured. Daily rhythm of excretion had a significant variation according to a signal analysis. The peak value at 22°C appears to be during the first hour of photophase both with morning and evening pulse birds, which indicates digestion at late dark phase. The evening pulse birds excreted more at night than the birds fed in the morning. At 5°C the excretion peak during the first photophase hour disappeared. Again, evening pulse birds excreted more at night than during the day. Significant excretion difference between T<sub>a</sub>'s was found only with morning pulse birds (p < 0.05). Pigeons had a clear diurnal T<sub>b</sub> rhythm. The lowest values of 38.5-39.0°C occur at midnight, and the peak values of 41-42°C during feeding sessions were observed. The total daily dropping mass was 20.1 g with morning pulse pigeons and 25.2 g with evening pulse pigeons, and water content of droppings were 14.6 g and 19.1 g, respectively. Regulatory interaction of shivering and digestion-related thermogenesis in pigeons is supported by the present finding of similar digestion timing at late dark phase, independent on time of food pulse and thermal load, and previous evidence for food retention in the crop.

Rashotte, M.E., Saarela, S., Henderson, R.P. & Hohtola, E. (1999) Shivering and digestion-related thermogenesis in pigeons during the dark phase. *American Journal of Physiology*, 277, R1579-R1587.

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## HUMAN MINUTE VENTILATION RESPONSES TO CARBON DIOXIDE LEVELS PRIOR TO AND FOLLOWING AN EXERCISE INDUCED HYPERHERMIA

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The control of ventilation during exercise is poorly understood. Minute ventilation ( $V_E$ ) can increase by as much as fifteen times during exercise, while normal metabolic mediators of ventilation are at or below resting levels. Elevated core temperature has been shown as a potential mediator of a hyperpnea in both resting and exercising humans. For resting subjects is not clear, however, if the ventilatory response to carbon dioxide changes with an actively induced hyperthermia, as it is known to occur for passively induce hyperthermia. The purpose of this study was to compare  $V_E$  responses to progressively elevated inspired carbon dioxide tensions between pre-exercise resting normothermic and post-exercise resting hyperthermic subjects. Six subjects (mean  $\pm$  SE, 27.5  $\pm$  1.3 years of age; body weight 72.8  $\pm$  1.6 kg; heights 1.8  $\pm$  0.8 m) performed a modified Read rebreathing test. During rebreathing the initial inspired carbon dioxide was 7%, oxygen was 43% with the balance from nitrogen. Each rebreathing was preceded by 1-2 min of hyperventilation. The rebreathing tests were conducted both before and after performing seated cycle ergometer exercise. Cycle ergometer workloads were increased from rest by 20W/2 min to steady state of 196.6  $\pm$  3.9 W. The highest workloads employed were 73.3  $\pm$  0.3 % of the subjects' previously obtained maximal attainable ergometer workload. The pre-exercise esophageal temperature of 36.62 $\pm$ 0.02°C was significantly increased both at the end of exercise by 1.51 $\pm$ 0.03°C ( $p<0.05$ ) and during the rebreathing by 0.84 $\pm$ 0.05°C ( $p<0.05$ ). The threshold point and slopes of the relationship of  $V_E$  plotted as a function of end-tidal carbon dioxide tension ( $P_{ET}CO_2$ ) were compared between the two conditions. From the normothermic to the hyperthermic condition, the  $P_{ET}CO_2$  threshold for  $V_E$  significantly decreased ( $p<0.05$ ) from 6.95  $\pm$  0.13 kPa to 6.15  $\pm$  0.10 kPa. The slope of the  $V_E$  vs.  $P_{ET}CO_2$  significantly increased ( $p<0.05$ ) from 15.63  $\pm$  1.28 L/min $\cdot$ kPa for normothermic subjects to 22.48  $\pm$  0.91 L/min $\cdot$ kPa for hyperthermic subjects. In addition, at a given  $P_{ET}CO_2$ , there was an elevated  $V_E$  in the hyperthermic versus normothermic condition. In conclusion, for resting humans previously rendered hyperthermic by exercise, there appears to be both a greater sensitivity to inspired carbon dioxide and a greater level of ventilation. The data supports the hypothesis that respiratory control centre output is increased for resting human subjects previously rendered hyperthermic by exercise.

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## DEVELOPMENT AND EVALUATION OF A CLOTHING SYSTEM FOR OFFSHORE INDUSTRY WORKERS IN COLD ENVIRONMENTS

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People working in the offshore environment in northern regions are exposed to harsh climatic conditions characterised not only by low air and water temperatures, but also by wind, high humidity, rain and snow. Cold environments affect the health, safety, comfort and performance of workers and cold interferes with work and may impair performance and productivity. Protection is needed against cold, wetness and physical hazards, and appropriate clothing should also be selected on the basis of the work activity involved. The development of work clothing for extreme work environments is a complicated process, in which protection and comfort properties have to be balanced and objective properties and subjective preferences have to be considered. The aim of this study was to develop a tool for the development, testing and evaluation of work clothing for offshore industrial workers. A further aim was to identify, on the basis of preferences indicated by offshore industry workers, a combination of materials, construction and design that would provide optimum solutions for work in cold and wet environments. **Methods:** The first step involved the specification of requirements using a modified concept-engineering model. This customer-centred process is used to clarify the end users' needs and wishes before detailed design and product development. This stage was performed in the course of individual interviews on board an oil production platform in the North Sea. The workers' preferred requirements for a new offshore work suit were established before a questionnaire, that aimed to identify the priority order of the requirements was sent out to a sample of workers. The next stages in the project involved the establishment of technical requirements, selection, testing and evaluation of materials, and prototype design. Prototypes were produced on the basis of the selected textiles and end-user requirements. During the final step the newly designed outer garments were compared with a reference outer garment using six test subjects in simulated work environments ( $T_a = 2^\circ\text{C}$  / wind speed  $5 \text{ m} \cdot \text{sec}^{-1}$ ). The test protocol comprised two-hour working-resting periods. One bout of 30-min cycle exercise was followed by a 30-min rest, a 30-min exercise period that included lifting and carrying, and a final 30-min rest. Between the working and resting periods the subjects were exposed to rain, simulated by exposing them, fully clothed, to a water shower. Physiological variables; skin temperatures, heart rate, humidity accumulation and subjective evaluation were recorded throughout the tests. In this project the systematic design process involved defining requirements, selecting materials, designing the garments and testing prototypes. This study focuses on improvements in resistance to air penetration, water permeability, insulation properties and moisture transport capacity in relation to the physiological parameters measured. The clothing physiology tests demonstrated improved properties of the new garments. Both the thermal protective properties and the subjective evaluations of the garments were improved in comparison with current models. The tests further demonstrated the necessity of planning the protective clothing system as a total system, including underwear, middle layer clothing and outer garments.

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## SELF-REPORTED ASTHMA AND EXERCISE-INDUCED RESPIRATORY SYMPTOMS IN MARATHON RUNNERS AND CROSS-COUNTRY SKIERS

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Asthma and asthma-like symptoms are frequently reported among elite runners and cross-country skiers. These sports both involve high ventilatory activities with different competition seasons, and the exposure to certain environmental factors may contribute to the development of asthma. Though there are strong genetic influences on the occurrence of asthma, the prevalence of the condition remains predominantly determined by the environment. Previous studies on runners and skiers have principally involved elite athletes and control groups not involved in active competitive sports. However, mass-participation marathons and cross-country ski races mainly involve non-elite subjects, and the purpose of this study was to compare the prevalence of self-reported asthma and exercise-induced respiratory symptoms in non-elite runners and skiers. The skiers and runners are exposed to different climatic conditions during their competition seasons and we hypothesised that the prevalence of asthma and respiratory symptoms in skiers would be higher than in runners because of exposure to colder and dryer winter climate. A questionnaire was mailed to the entrants of a marathon and a cross-country ski race in Norway and the 827 subjects whose main sport activity was running (n=512) or skiing (n=315) were included in the study. The questionnaire was developed from an existing list of questions, which had already been used in multinational studies. It was modified for this study in order to evaluate the prevalence of self-reported asthma as diagnosed by a physician and associations between respiratory symptoms (during and/or after exercise during the last year) in relation to exercise and climate. The prevalence of physician-diagnosed asthma was 7.1% in runners and 10.6% in skiers and did not differ significantly. However, asthma was more frequent in women (15.5%) than in men (7.4%) and more prevalent in the age group 18-39 years (12.2%) than in older subjects (6.4%). Among the exercise-induced respiratory symptoms, cough was the most common symptom in both groups and the prevalence was dependent on age, amount of training and climatic conditions. In subjects exercising for zero to three hours per week (n=133) in the three months previous to the marathon and ski competitions, no differences in prevalence of cough were found between the runners and skiers. However, in subjects exercising more than three hours per week (n=675) a significantly higher frequency of cough was registered among skiers (40.3%) than in runners (23.2%). A higher frequency was also registered in subjects living in municipalities with the lowest January temperatures ( $T_a$ ). Cough was reported by 38.0% ( $T_a = -12$  to  $-8^\circ\text{C}$ ), 31.4% ( $T_a = -8$  to  $-4^\circ\text{C}$ ) and 23.1% ( $T_a = -4$  to  $4^\circ\text{C}$ ) of the subjects living in the three climatic areas. In terms of amount of training, no differences in cough were registered in the subjects who trained for zero to three hours in the different areas (25.0%, 28.8% and 24.0%). In subjects who trained for more than three hours per week the corresponding values were 39.7%, 31.9% and 23.2%. This demonstrates the importance of exercise level and climate on exercise-induced respiratory symptoms.

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## **EFFECT OF CLOTHING ON COLD-INDUCED VASODILATATION (CIVD) RESPONSE AND SUBJECTIVE THERMAL LOADS DURING REPEATED FINGER COOLING**

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In workers in cold environments such as refrigerated warehouses, food processing facilities and outdoors in cold weather, excessive cooling of fingers and toes have been frequently reported. In such cold work places, the workers are likely to handle frozen materials through cotton gloves or cold protective-gloves they wear, or touch a frozen fish or meat directly with their hands, or immerse their fingers in cold-water. In almost all cases, their fingers and hands are repeatedly and intermittently cooled, with rests and pauses in between. However, there have been so far only a few studies on the effects of repeated or intermittent peripheral cooling. The objective of this study was to investigate how repeated and intermittent finger cooling affects cold-induced vasodilatation (CIVD) response and finger pain and thermal sensations under different clothing conditions. Seven young men aged 23 to 24 years immersed their right index fingers in stirred water at 10°C for 10 minutes. This immersion procedure was repeated five times under ambient temperature of 20°C and relative humidity of 50%. Each cold-water immersion was followed by a 5-minute rest under the same climatic condition. This repeated cold-water immersion experiment was carried out on different days under three clothing conditions: light (pants, T-shirt, shorts and socks), medium (light clothing plus shirt and trousers) and heavy clothing (medium clothing plus jacket). Under the heavy clothing condition, marked CIVD response occurred and the CIVD reactivity did not significantly change upon repetition of cold-water immersion. The finger skin temperature during each post-immersion rest also tended to recover quickly to the pre-immersion level. Under the light clothing condition, however, the CIVD response weakened continuously upon repetition of immersion and the response in some subjects almost disappeared during the final immersion. The recovery rate of finger temperature during each post-immersion rest tended to decrease continuously upon repetition of immersion. Under every clothing condition, finger pain sensation rapidly increased during each immersion, but it completely disappeared during each post-immersion rest period. Finger cold sensation also rapidly increased during each immersion, but it was replaced by a warm or slightly warm sensation during each rest period. These subjective sensations during the immersion and post-immersion periods had no significant differences between clothing conditions. The present study suggests that light clothing in a cool environment may weaken CIVD reactivity during repeated finger cooling and delay the recovery of finger temperature during post-immersion rest periods. It also suggests that under such conditions, subjective judgments such as absence of finger pain and occurrence of warm sensations during post-immersion rest may not be reliable indicators of the risk of progressive finger cooling and frostbite formation.

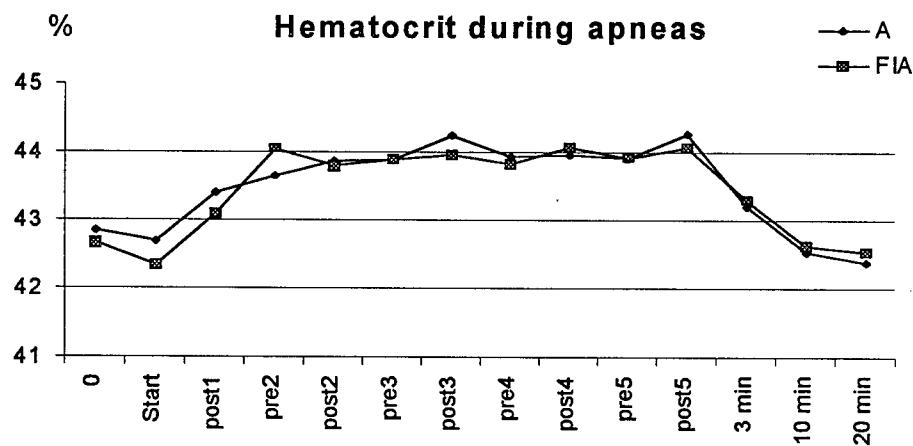
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## DOES FACIAL CHILLING AUGMENT THE HEMATOCRIT INCREASE SEEN AT HUMAN APNEIC DIVING?

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It has been shown that an increase in Hct and Hb accompanies apneic diving (Hurford et al., 1990) or apnea with face immersion in humans (Schagatay et al., submitted). This increase appears to be caused by spleen contraction, as it is not observed in splenectomized subjects (Schagatay et al., submitted). It is known from the cardiovascular diving response that facial chilling increases the reductions of heart rate and skin blood flow during apnea. We focused in the present study on the neural input triggering the hematological response. Eight subjects, trained apneic divers or subjects with good breath holding ability (>2 min), volunteered for the study. The subjects rested in the prone position for 30 min before performing apneas. The subjects performed two series of five apneas of a fixed near maximal individual duration, one series in air (A) and one with facial immersion in 10°C water (FIA). Apneas of each series were spaced by 2 min resting intervals. The two series were separated by at least 20 min of rest and their order weighted. Venous blood samples were collected from a catheter inserted in the arm before tests. Hct and Hb were analysed directly with standard methods. We found a transient increase of the Hct in both apnea series. During A, Hct increased from 42.7% before apneas to 44.3% after the fifth apnea ( $p<0.05$ ), and had returned to baseline after 10 min (Figure). During FIA, Hct increased from 42.3 to 44.1% ( $p<0.05$ ; Figure). The response pattern was the same irrespective of the cold stimulus (NS; Figure). This pattern was repeated by the Hb values. We conclude that, unlike the cardiovascular diving response, the hematological response is triggered by the apnea stimulus only, thus not fortified by facial chilling.



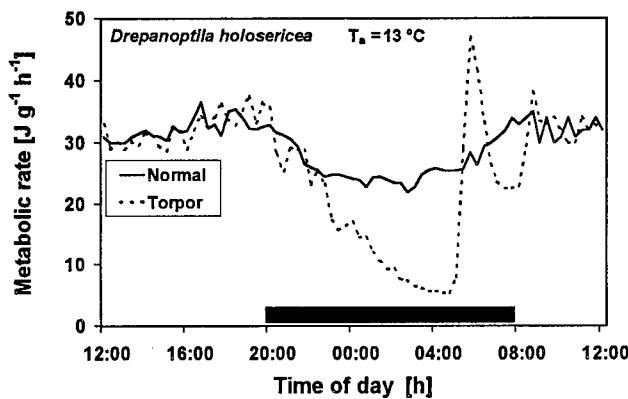
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## HETEROTHERMIA IN PIGEONS AND DOVES EXTENDS THEIR ECOLOGICAL LIMITS

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Pigeons and doves (Columbidae) occur in almost every habitat worldwide, having a striking ability to use different ecological niches. It is therefore intriguing to compare the physiological characteristics of different species with regard to the wide range of abiotic factors they are adapted to. In quantifying the influence of habitat on physiology, two key aspects were investigated and presented in the study; firstly, energy metabolism (M) because it reflects the total costs of living (such as locomotion, digestion, thermoregulation); and secondly body temperature ( $T_b$ ) as an important means of physiological adaptation in endotherms. The ability to regulate  $T_b$  at stable, high levels provides birds with a considerable independence of ambient temperatures, but it contributes considerably to their energetic demands. M was measured using standard methods of gas analysis in a variety of columbids from various habitats. At the same time,  $T_b$  - regulation of these species was investigated by telemetry transmitters and thermocouples. This paper will give examples of physiological regulation of small species from hot and arid habitats (Diamond Dove *Geopelia cuneata*, Namaqua Dove *Oena capensis*, body mass 30 – 40 g) and of an obligate frugivore from rainforest habitats (Cloven-feathered Dove *Drepanoptila holosericea*, 200g). The desert species not only face extreme temperature conditions but also unpredictable food and water availability. The fruit-dove is restricted to the island of New Caledonia, where it is also probably confronted with food and energy shortage situations due to variable fruit availability. Cloven-feathered Doves have only limited access to fruiting trees, even if the birds are partly nomadic. All species investigated had a variable but regulated  $T_b$  rather than metabolically "defending" a strictly defined, constant  $T_b$ . Compared to the mean "normothermic"  $T_b$  for birds (38 – 41 °C), they regulate  $T_b$  in hypothermic (25 to 37 °C) as well as in hyperthermic (up to 45 °C) states. Hyperthermia is used by the small xerophilous doves to reduce heat stress. By maintaining their  $T_b$  above ambient temperature ( $T_a$ ) at most times, these species are able to reduce their total daily water loss by 10 % and minimize the time spent at the waterhole. Hypothermia, on the other hand, is used by both the small and the large species to conserve energy under adverse conditions. One physiological response is that when deprived of food, the small Namaqua and Diamond Doves are able to lower their rest  $T_b$  by 4 to 7 °C compared to normal night-time levels. This reduces their total daily energy consumption by 10 %. The same strategy is used by the Cloven-feathered Doves; however, they undergo torpor (lowest  $T_b$  recorded was 24.8°C with spontaneous arousal at the end of night phase). During torpor, M is reduced by 67 % compared to normal night-time values (Figure: M of Cloven-feathered Doves with nocturnal hypothermia (—) and torpor (---). The dark bar represents the night phase.). This is the first evidence for "true" torpor for pigeons. High physiological flexibility, especially heterothermia, is a strategy which probably contributes considerably to the columbids' successful colonisation of different habitats around the world.



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## DEVELOPMENT OF THERMOREGULATORY COMPETENCE, CIRCADIAN PERIODICITY AND CONTROL OF ENERGY BALANCE IN RAT PUPS: A REVIEW

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Despite their neural immaturity suckling-age rats show an endogenous circadian rhythm with torpor-like decreases of metabolic rate (MR) and core temperature (Tc) under cold loads but not at thermoneutrality (TN) (1,2). This rhythm develops in the first postnatal days and ceases in the 3<sup>rd</sup> week, i.e. long before the adult rhythm develops (1,3). The daily minimum of the juvenile rhythm is associated with a decrease in sympathetically mediated thermoregulatory thermogenesis (TT) in brown adipose tissue and a blunted response to sudden drops of Ta, which are, however, not due to an impairment of TT (2,3). The notion that the juvenile circadian rhythm is a mode of energy saving and not the indication of thermoregulatory incompetence (2) was confirmed when treatment with recombinant leptin, a hormone produced by adipose tissue and signaling the size of energy stores to the brain, became possible (4). Leptin-treatment under cold load results in a suppression of the daily drop of MR and Tc, as does the destruction of the leptin receptors in the arcuate nucleus, thus causing a higher energy expenditure and a reduced fat storage (4). Treatment of pups at TN causes an improvement in the TT capacity, but no change of basal MR and body fat stores (5). Various lines of evidence suggest that the central sympathetic outflow integrates the afferent commands provided by the thermosensors and by leptin and other signals reflecting the metabolic status of the organism and, thus, forms the common underlying mechanism by which changes in energy balance and in the TT capacity are linked to each other (3). Changes in the central sympathetic nervous system might, therefore, also underly the influences of the pre- or early postnatal thermal or nutritional environment which are responsible for the development of normal energy balance regulation or the programming of life-long aberrations, like dispositions for obesity and related metabolic disturbances (3,6,7,).

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## NITRIC OXIDE AND ANGIOTENSIN II: NEUROMODULATORS IN THERMOREGULARTION DURING EXPOSURE TO COMBINED HEAT AND HYPOHYDRATION STRESS

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In mammals, perturbation in body fluid homeostasis interferes with the ability to cope with thermal stress. With the hypothalamus representing the major integrative center, the knowledge of its osmo- and thermoregulatory interactions is still confined primarily to phenomenology manifested by whole body heat defense responses. Based on the involvement of the central renin-angiotensin (AngII) system and nitric oxide (NO), individually, in fluid balance and thermoregulation, the purpose of this work was to assess the involvement of NO in the integration between osmo- and thermoregulatory circuits, and to define the mutual effects of NO and AngII. For this purpose, heat defense responses - vasodilatation, evaporative cooling (salivation threshold), blood pressure and endurance - were measured in conscious heat stressed (39°C) rats (*Rattus norvegicus*, Sabra strain, albino var.) following administration of 7-nitroindazole (Ni; 100nm in a bolus), an antagonist of neuronal NO synthase, AngII (100pm), saline or both, into the cerebrolateral ventricle, in the following groups: heat acclimated (AC)-30d, 2d, and non-AC either euhydrated or hypohydrated (-10% of body weight). All drugs were dissolved in saline to final volume of 5μl. Body temperature (Tc), skin temperature (Tsk), and blood pressure were monitored on-line using a computerized data acquisition system. Our data support a role played by NO during exposure to individual as well as combined thermal and osmotic stress, in a biphasic manner, compared to the acclimation state, and in opposite directions in the different hydration states. The role of AngII is proven particularly following 30 d of acclimation. The effects of the two modulators, both separately and combined, fit with the model of Millatt et al. (1999) explaining AngII-NO interactions by differential activation/inhibition of AT1-AngII receptors, and a direct NO effect.

		Ni (100nmol)	AngII (100pmol)	Ni + AngII
Control	endurance	-	-	↓
	VTsh	↓	↓	-
	STsh	↓	↓	↓
STHA	endurance	↑	↓	-
	VTsh	-	-	-
	STsh	-	-	↑
LTHA	endurance	↓	↓	-
	VTsh	-	↓	↓
	STsh	-	↓	↓

Millat, L.J., Abdel-Rahman, H.M. & Siragy, H.M. (1999) Angiotensin II and nitric oxide: a question of balance. *Regulatory Peptides*, 81(1-3), 1-10.

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## NITRIC OXIDE AND ANGIOTENSINII - NEUROMODULATORS IN THERMOREGULARTION DURING EXPOSURE TO COMBINED HEAT AND HYPOHYDRATION STRESS

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		Ni (100 nmol)	AngII (100 pmol)	Ni+AngII
Control	endurance	-	-	↓
	VTsh	↑	↓	-
	STsh	-	↓	↓
STHA	endurance	↑	↓	-
	VTsh	-	-	-
	STsh	-	-	↑
LTHA	endurance	-	↓	-
	VTsh	-	↓	↓
	STsh	-	↓	↓

Millat, L.J., Abdel-Rahman, H.M. & Siragy, H.M. (1999) Angiotensin II and nitric oxide: a question of balance. *Regulatory Peptides*, 81(1-3), 1-10.

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## THE EFFECT OF RAPID COOLING ON THE COURSE AND PROGNOSIS OF EXERTIONAL HEAT STROKE - TWO CASE REPORTS

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Heat stroke, an occasionally fatal disease, is the most serious of conditions associated with elevated body temperature. When it occurs during exercise it is regarded as exertional heat stroke (EHS). The elevated body temperature becomes a noxious agent, causing damage to the body's tissues, and giving rise to a characteristic multi-organ clinical and pathological syndrome. Two cases of EHS in which treatment was administered at different time intervals are presented.

**Case 1:** An 18-year-old previously healthy male participated in a pre-draft military selection trial during a hot summer day. The trial consisted of short and long distance running with various back loads, and various other interval exercises. After two hours of high intensity exercises he collapsed. No treatment was administered on site. The patient was evacuated to a hospital, arriving at the emergency room (ER) 60 min after collapse. Upon arrival to the ER, he was unconscious with a rectal temperature ( $T_{re}$ ) of 40.5°C. Only then was treatment by tap water cooling and IV fluids initiated. The patient regained consciousness within a few hours, albeit remaining lethargic for several more days. Two days after the collapse he developed severe rhabdomyolysis with extremely high creatine kinase (CK) levels of 198,000 IU·L<sup>-1</sup>, and marked swelling and pain of the right quadriceps and gluteus muscles. Marked hepatic and renal disturbances were noted as well. The patient was treated conservatively with laboratory results returning to normal values after 14 days.

**Case 2:** A 20-year-old previously healthy male participated in a similar pre-draft military selection trial as case 1, taking place during warm weather, and collapsed as well.  $T_{re}$  measured on site was above 42.5°C (the end of the thermometers scale). Cooling treatment, namely splashing copious amounts of water on his body, was immediately initiated. When he arrived at the ER 40 min later, the patient was psychotic, aggressive, and with a  $T_{re}$  of 40.0°C. Treatment consisted of continued cooling, IV fluids, and IM Haloperidol. Within five hours from his collapse the patient was up and walking in good condition. There were no notable events during hospitalization, apart from relatively moderate CK and liver enzyme elevations.

**Conclusions:** Rapid recognition and treatment of EHS (case 2) can dramatically alter its course and prognosis, which are in direct relationship with the area under the curve of the hyperthermic period. Proper treatment should consist of liberally splashing copious amounts of water on the patient. Medical staff accompanying military training or athletic competition should be aware of the risk of EHS, as should the commanders and organizers of such events. A high level of suspicion must be maintained and proper means for cooling EHS victims kept at hand. Nevertheless, the prevention of EHS, which requires the application of relatively simple safety regulations, should be sought.

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## ACETYLCHOLINE RELEASED FROM SUDOMOTOR NERVES IS CAPABLE OF CONTRIBUTING TO CUTANEOUS VASODILATION DURING HEATING IN HUMANS

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Inhibition of nitric oxide synthase (NOS) reduces the magnitude of cutaneous vasodilation during a heat stress in humans. Given that acetylcholine is released from sudomotor nerves during whole-body heating, coupled with the observation that acetylcholine stimulates nitric oxide production leading to vasodilation, it is possible that acetylcholine released from sudomotor nerves is capable of contributing to cutaneous vasodilation during a heat stress via nitric oxide related mechanisms. To test this hypothesis, in seven subjects skin blood flow and sweating rate were simultaneously monitored over three microdialysis membranes placed in the dermal space of forearm skin. One membrane was perfused with the acetylcholinesterase inhibitor neostigmine (10  $\mu$ M), the second membrane was perfused with the NOS inhibitor N<sup>G</sup>-nitro-L-arginine methyl ester (L-NAME; 10 mM) dissolved in the aforementioned neostigmine solution, while the third membrane was perfused with Ringer's solution (vehicle). Each subject was exposure to a minimum of 20 minutes of whole-body heating via a water-perfused suit. This perturbation increased average skin temperature from  $34.6 \pm 0.1$  to  $38.6 \pm 0.2$  °C ( $P < 0.05$ ) and sublingual temperature from  $36.9 \pm 0.1$  to  $37.3 \pm 0.1$  °C ( $P < 0.05$ ). Following the heat stress maximal skin blood flow at each site was identified via administration of 28 mM sodium nitroprusside through the microdialysis membranes. Skin blood flow was then normalized relative to maximal skin blood flow for that site.

Unit (% maximum SkBF)	Rest	$\Delta$ SkBF (I)	$\Delta$ SkBF (II)
SkBF (NEO)	$29.2 \pm 4.7^{*#}$	$12.8 \pm 3.2^{*#}$	$40.0 \pm 4.3^{*#}$
SkBF (control)	$19.5 \pm 3.1$	$7.6 \pm 2.7$	$39.4 \pm 2.9^{*#}$
SkBF (L-NAME + NEO)	$13.0 \pm 1.5$	$3.6 \pm 1.0$	$20.3 \pm 2.1$

SkBF: skin blood flow; NEO: neostigmine;  $\Delta$ SkBF (I): increase in SkBF from rest to a period early in the heat stress (i.e. prior to clear increases in SkBF at L-NAME site);  $\Delta$ SkBF(II): increase in SkBF from the rest to the end of heating. \* significantly different from control site, # significantly different from L-NAME+NEO site. ( $P < 0.05$  for both).

The observation that the increase in skin blood flow early in the heat stress [i.e.  $\Delta$ SkBF (I)] at the neostigmine treated site was significantly greater than at the control site suggests that acetylcholine released from sudomotor nerves is capable of modulating cutaneous vasodilation early in the heat stress. Moreover, the observation that early in the heat stress skin blood flow at the L-NAME + neostigmine treated site was significantly less than skin blood flow at the neostigmine treated site suggests that the elevation in skin blood flow at the neostigmine treated site was NOS dependent. In contrast, the lack of difference in skin blood flow between the neostigmine and control sites at the end of heating suggests that acetylcholine released from cholinergic nerves does not contribute to cutaneous vasodilation during moderate whole-body heating.

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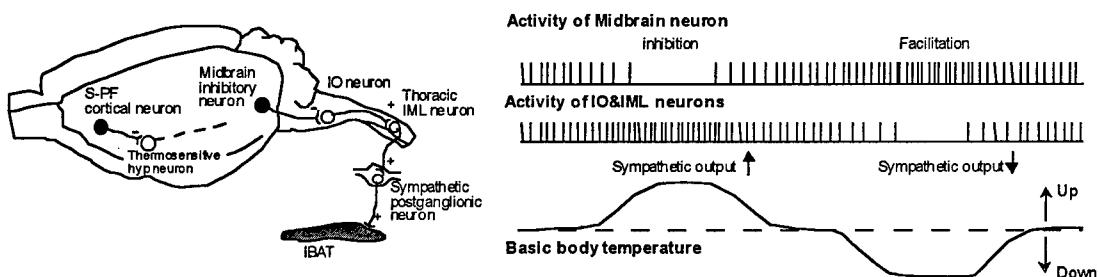
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## CENTRAL EFFERENT CONTROL OF NONSHIVERING THERMOGENESIS IN RATS

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As summarized in the Figure, we have recently reported that, in rats, neurons in the lower midbrain tonically inhibit nonshivering thermogenesis (NST) of the interscapular brown adipose tissue (IBAT) via inhibitory synaptic connections with the inferior olive neurons of which outputs stimulate the IBAT NST through activation of the thoracic intermediolateral (IML) neurons. Removal of the midbrain tonic inhibitory mechanism (MTIM) on the NST, therefore, increases IBAT and rectal temperatures through disinhibition-induced activation of the central sympathetic nervous system. It is, however, not known whether and how the hypothalamus exerts its influence on the MTIM. The aim of the present experiment was to examine this question using urethane-anesthetized (1.0 - 1.2 g/kg, ip) male Wistar rats. Temperatures of the rectum (Trec), IBAT ( $T_{IBAT}$ ) and tail skin (Tskin) were monitored with copper-constantan thermocouples after bilateral procaine microinjections (10%, 1.0  $\mu$ l/site) into the midbrain to transiently remove the MTIM before and during hypothalamic cooling or warming in anesthetized animals. In conscious animals, procaine was also microinjected into the lower midbrain with and without decerebration. The magnitude of the midbrain procaine-induced  $T_{IBAT}$  increase was larger ( $0.71 \pm 0.15$  °C) and smaller ( $0.39 \pm 0.02$  °C) during hypothalamic cooling and warming, respectively, compared with that during thermoneutral hypothalamic temperature ( $0.50 \pm 0.10$  °C).  $T_{IBAT}$  and Trec increases by the midbrain procaine in conscious decerebrated rats reached  $41.37 - 42.52$  °C while those in non-decerebrated conscious rats were between  $37.63 - 37.80$  °C. These results indicate that the hypothalamus exerts directly or indirectly its modulator influence on the MTIM.

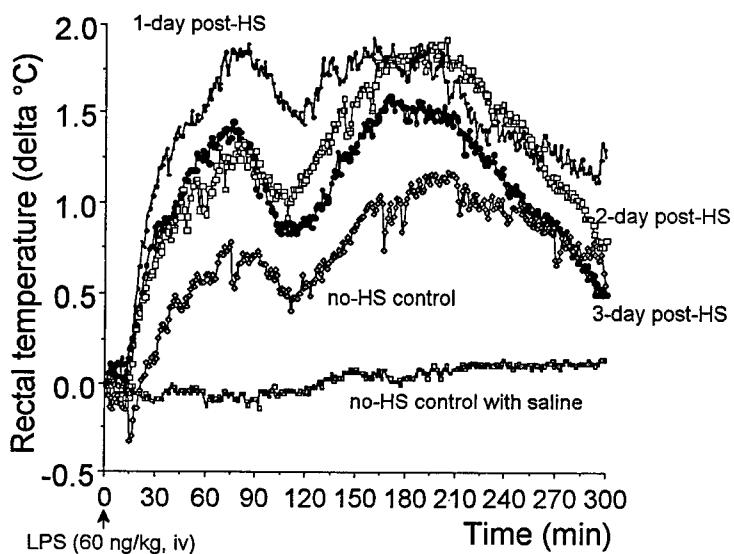


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## ENHANCED LPS-FEVER FOLLOWING HYPERTHERMIC STRESS IN RABBITS

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Whether higher than normal body temperature is beneficial or detrimental to animals and humans is a matter of debate. The reason for this debate is unclear. However, the conflicting results seem to come from different experimental conditions used, e.g., magnitude of hyperthermia, duration of hyperthermic condition, etc. In the present experiments, we attempted to examine a question whether and how hyperthermia affects host defense responses induced by endotoxin lipopolysaccharide (LPS, *Escherichia coli* 011:B4) using male Japanese white rabbits. Animals were made hyperthermic (rectal temperature, Trec, of 43 °C) by placing them in a hot chamber for 2-3 h. They were then removed from the chamber and made to recover under a room temperature of 25 °C. Three groups of heat stressed (HS) animals were prepared: 1 - day, 2 - day and 3 - day post - HS. These animals together with non - HS control animals were given LPS (60 ng/kg, iv) and Trec was monitored. Animals of 1 - day, but not 2 - day and 3 - day post - HS, showed significantly larger LPS fever (28.5% in terms of fever index) than those of controls (see the Figure). However, there was no difference in fever index between 1 - day post - HS and control animals when fever was induced by interleukin - 1 $\beta$  (240 ng/kg, iv). There was also no difference in levels of the cerebrospinal fluid prostaglandin E2 between 1 - day post - HS and control animals. A higher count of circulating neutrophils was observed in 1 - day, but not 2 - day and 3 - day post - HS animals. Levels of plasma tumor necrosis  $\alpha$  during LPS fever were higher in 1 - day post - HS than control animals. These results indicate that the enhanced LPS fever observed in 1 - day post-HS animals may be caused by altered circulating neutrophils. They also implicate the possibility that 1 - day post - HS animals may be more susceptible to infections than control animals.



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## MECHANISM OF SEVERE HYPOTHERMIA INDUCED IN A COOL ENVIRONMENT IN A YOUNG FEMALE PATIENT

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A 17-year-old female patient (height 151.9 cm, body mass 52.3 kg) suffering from severe hypothermia was admitted to the Pediatrics Department, Kanazawa University Hospital in winter (February) of 1998. Body temperature (axillary temperature), heart rate and systolic and diastolic arterial blood pressures at admission were 31.8 °C, 40 bpm and 84 and 42 mmHg, respectively. There were no particular abnormalities in the other routine physical examinations except for her slow body movement due to hypothermia. In subsequent studies, thermogenic hormone levels, such as plasma thyroid hormones and urinary catecholamines, were judged to be within normal ranges and brain MRI showed no specific changes in the hypothalamus and pituitary regions. According to a questionnaire, the patient had not noticed a fall in her core temperature during the episode of severe hypothermia, while, in a hot environment and during exercise, she could feel hot and perspire. We then investigated thermoregulatory function of the patient after obtaining informed consent of the patient and her parents in summer of the same year. The patient, wearing T-shirt and shorts, entered a climatic chamber and was seated on a chair at an ambient temperature (Ta) of 28 °C and a relative humidity of 60%. Rectal and skin (7 sites) temperatures, heart rate and oxygen consumption were measured. After a 30-min rest, the Ta of the chamber was decreased to 24 °C in 20 min and the new Ta was maintained for following 100 min. The rectal temperature of the patient gradually decreased even at the Ta of 28 °C and became 35.6 °C at the end of the test. The fall in rectal temperature was associated with reductions in heart rate and skin temperatures. Clear vasoconstriction was seen only in the foot when rectal temperature reached ca. 36.0°C. Oxygen consumption of the patient did not increase regardless of the hypothermia, but slightly decreased. Indeed, no shivering was induced throughout the test. In a different series of studies, the patient's serum was intraperitoneally injected into rats, which were chronically implanted with a temperature transmitter for telemetry system. The serum produced a marked and short-lasting fall in core temperature. The fall in core temperature was consistent when dialyzed serum (69 kD cutoff) was injected into rats. Taken together, it appears that the threshold core temperatures for thermogenesis and vasoconstriction of the patient shifted to extremely low levels, which then resulted in the severe hypothermia in a cool environment. We speculate that the patient may have produced unknown cryogenic substances with a large molecular size.

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## **EFFECT OF STRENUOUS LIVE-FIRE FIREFIGHTING DRILLS ON HEMATOLOGICAL AND PSYCHOLOGICAL MEASURES**

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Fire fighting activity involves strenuous physical work in heavy protective gear and often exposes fire fighters to extreme radiant heat loads. Thus, fire fighting presents an excellent model to study physiological and psychological responses to acute, extreme heat stress in humans. The purpose of this study was to describe the effects of strenuous live-fire fire fighting drills on selected hematological and psychological variables and to document the extent to which these variables recovered following 1.5 h of recovery. The extent of recovery is particularly important in this population as fire fighters often work a 24 hour shift and may be required to respond to another fire at any time. Eleven apparently healthy, male, professional firefighters performed three trials of a standardized set of fire fighting tasks in a training structure that contained live fires. Blood was drawn prior to the start of the tasks, immediately post fire fighting activity, and after 90 min of recumbent recovery. Psychological data were collected at the end of each trial. Plasma volume decreased by 15% immediately post fire fighting activity, but returned to baseline following recovery and aggressive rehydration. During the recovery period the fire fighters consumed an average of about 1.5 L of cold water. The decrease in plasma volume immediately following fire fighting activity was accompanied by increases in hemoglobin and hematocrit. Consistent with the observed hemoconcentration, several of the nineteen blood chemistry variables increased significantly immediately post fire fighting activity, and returned to baseline values following recovery. Blood glucose values were significantly lower than pre-test or post-fire fighting values after 90 minutes of recovery. These data emphasize the need for aggressive fluid replacement following strenuous fire fighting activities and suggest that fire fighters may benefit from carbohydrate replacement prior to subsequent activity.

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## LATITUDINAL COLD ADAPTATION VERSUS SEASONAL COLD ACCLIMATISATION IN LUGWORMS (*A. MARINA*)

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The temperature dependence of mitochondrial functions were investigated in cold adapted intertidal lugworms, *Arenicola marina* (polychaeta), from the White Sea (subpolar summer) and cold (winter) or warm (summer) acclimatised lugworms from the North Sea (boreal). Mitochondria were isolated from the body wall tissue after animals were killed by decapitation.

Eurythermal adaptation to lower mean annual temperatures in White Sea animals is reflected by an increase in aerobic capacity compared to North Sea summer animals. Mitochondria from subpolar lugworms are characterised by a higher activity of cytochrome c-oxidase and NADP dependent isocitrate dehydrogenase as well as a rise of their maximal rates of substrate oxidation (nmol·min<sup>-1</sup>·mg<sup>-1</sup> mitochondrial protein) and a reduction of the value of activation energy (Ea) for the oxidation of cytochrome c. Moreover, White Sea lugworms display 2.4 times higher mitochondrial volume density in the muscle tissue than summer animals from the North Sea. The rise in aerobic capacity is mirrored by a downward shift of the low critical temperature (Tc). However, the oxygen demand of the whole animal increases due to the rise in mitochondrial maintenance costs, followed by a shift of the high Tc to lower temperatures. We hypothesise that this shift is minimized by a rise in Ea values for the decarboxylation of isocitrate and a lower activity of citrate synthase (CS). In contrast to cold adaptation in a latitudinal cline, seasonal acclimatisation to winter conditions in North Sea lugworms led to a rising activity of CS. Phosphorylation efficiency and mitochondrial coupling were also higher in winter than in summer specimens (both from the North and the White Seas). State 4 respiration in the presence of oligomycin (state 4ol), an inhibitor of mitochondrial F<sub>0</sub>F<sub>1</sub>-ATPase, quantifies the proton leakage rates through the inner mitochondrial membrane. No difference between proton leakage rates were seen in cold adapted White Sea lugworms and cold acclimatised winter animals from the North Sea. However, state 4ol respiration rates in summer animals from the North Sea were significantly reduced. Nevertheless, the percentage of oxygen needed to feed the proton leakage during state 3 respiration was lowest in winter animals compared to summer animals from the North or White Seas due to elevated state 3 respiration rates in winter lugworms. Cold adaptation or acclimatisation leads to a decrease in the low critical temperature threshold, which is characterised by the onset of anaerobic metabolism. It seems that a rising efficiency of aerobic energy production in winter animals is associated with metabolic depression at the expense of regulatory flexibility. In contrast, adaptation of White Sea lugworms to lower mean annual temperatures and to larger temperature fluctuations leads to an increased aerobic capacity, but at the expense of a higher metabolic rate.

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## USE OF TELEMETRY TO EVALUATE THE IMPACT OF SUMMER HEAT STRESS ON CORE BODY TEMPERATURE OF CATTLE

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Exposure to summer heat stress in the absence of shade can have significant impact on thermal status of feedlot cattle, especially in Midwest, USA. Few studies have considered the direct impact of solar radiation on thermal status. Recent advances in telemetry technology provide continuous monitoring of core body temperature in a field environment, allowing for assessment of relationships with ambient endpoints. A 14-day study was conducted during peak summer heat to record core body temperature via radiotelemetry and simultaneously monitor ambient conditions. Twelve Angus x Simmental steers (533 kg average body weight; *Bos taurus*) were maintained in a feedlot environment without access to shade, and provided a typical finishing diet and water *ad libitum*. Core body temperature (Tcore) was continuously recorded for each animal using a telemetric temperature transmitter (CowTemp Model BV-010; Innotek, Inc.) in the peritoneal cavity. Data loggers (Hobo H8 Pro; Onset Computer Corp.) were used to record air temperature (Ta) and percent relative humidity, together with black globe temperature (BG) for assessment of radiant heat load. Both temperature-humidity (THI) and black globe temperature-humidity (BGTHI) indices were calculated using these recorded ambient values. Initial comparison of animal and environment values showed greater correlation between day values alone than day-night values combined. Therefore, all comparisons use averaged group values for day only. Daily high Ta and BG values ranged from 26-37 and 36-48 °C, respectively, with lows for both values ranging from 14-27 °C. High THI values reached danger – emergency zones from day 9 to 16. Likewise, Tcore exhibited a progressive increase from days 9 to 14. Breaking points for linear increases in Tcore for the entire study period were 23.5 and 31.8 °C for Ta and BG values, respectively. Best-fit relationships between Tcore and all environmental variables, using all day values, were second-order polynomial regressions. Correlation (R) between Ta and Tcore was 0.85, and increased only to 0.86 with a 1 hour Tcore delay behind Ta. In contrast, R for BG and Tcore increased from 0.75 to 0.86 with a similar shift. Relationships between THI and BGTHI with Tcore improved when Tcore was shifted 2 hours behind the indices. Product values of Ta x BG and THI x BGTHI with Tcore yielded the highest R values (i.e., 0.89 – 0.90) when Tcore was shifted behind the environmental stressor index by 1 hour. These results indicate telemetric transmitters can be used to reliably predict changes in thermal status within the natural environment, and identifies that the best prediction is achieved with a 1-2 hour delay in core temperature behind changes in ambient thermal conditions.

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## NITRIC OXIDE IN THE CONTROL OF BODY TEMPERATURE AND FEVER

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Fever is a phenomenon characterized by a raised thermoregulatory set point that leads to an elevation in body temperature (T<sub>b</sub>). It is well known that fever can be initiated by a number of agents including endotoxin (LPS), viruses, yeast and Gram-positive bacteria. Considerable efforts have been made to identify the mechanisms of fever, but they still remain only partially understood. Recently, a new biologically active molecule has been described, *i. e.*, the gaseous compound nitric oxide (NO). This molecule started a revolution in the understanding of the physiological systems and has been shown to participate of several physiological and pathophysiological manifestations, including thermoregulation and fever. A growing body of evidence supports that NO plays a role in thermoregulation under euthermic conditions. In this context, we and others have provided evidence that NO plays different thermoregulatory effects by acting in the periphery and in the central nervous system (CNS). This notion is based on the opposite results obtained by injecting pharmacological modifiers of the NO pathway systemically or intracerebroventricularly. Accordingly, peripheral NO might increase thermogenesis, leading to an increase in T<sub>b</sub>, and yet increase heat loss mechanisms (cutaneous vasodilation, panting and sweating), producing a reduction in T<sub>b</sub>. The thermoregulatory effect of the systemic inhibition of NO synthesis depends, thus, on the prominent thermoregulatory mechanism in the species tested, ambient temperature, among other factors. Accordingly, systemic inhibition of NO synthesis has been shown to decrease T<sub>b</sub> in rats, a fact that seems to be associated with an impaired thermogenesis (Branco et al., 1997; Steiner et al., 1998), whereas systemic inhibition of NO synthesis increases T<sub>b</sub> in rabbits, a response which seems to result from a reduced respiratory heat dissipation (Mathai et al., 1997). Moreover, inhibition of NO synthesis in the CNS has been shown to lead to a slight increase in T<sub>b</sub> (Branco et al., 1997; Steiner et al., 1998), which is likely to be associated with an increase of the sympathetic tonus. As to fever, evidence has accumulated that peripherally acting NO is likely to be a signaling molecule for the development of fever since it has been reported that systemic administration of inhibitors of NO synthesis impairs fevers induced by LPS in rats and guinea pigs (Scammell et al., 1996), IL-1 in rats (Reimers et al. 1994; Roth et al., 1998), MDP in guinea pigs (Kamerman & Fuller, 2000), yeast in rats (Ataoglu et al., 2000) and even psychological stress in rats (De Paula et al., 2000). On the other hand, intracerebroventricular administration of NOS inhibitors enhances fever in rats and rabbits, suggesting that NO is an antipyretic molecule by acting in the CNS (Almeida et al., 1999). Although the summation of NO actions in the CNS results in antipyresis, NO may also be a pyretic molecule in some specific brain regions, such as the OVLT.

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## NITRIC OXIDE IS AN ANTIPYRETIC MOLECULE IN THE VENTROMEDIAL PREOPTIC REGION OF THE RAT BRAIN

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We tested the hypothesis that nitric oxide (NO) acts in the ventromedial preoptic (VMPO) region modulating fever. To this end, body core temperature (Tc) of awake, freely moving rats was monitored by biotelemetry before and after pharmacological modulation of the NO pathway. The animals were equipped with a guide cannula for intra-VMPO microinjections, which was implanted under tribromoethanol (250 mg/kg, ip) anesthesia. Nitrite/Nitrate and cGMP levels in the AV3V region (obtained from decapitated rats), where the VMPO is located, were also determined. Intra-VMPO microinjection of the nonselective NOS inhibitor L-NMMA (12.5 µg) did not affect basal Tc, but it anticipated the onset of LPS fever, indicating that NO plays an antipyretic role in the VMPO. In agreement, intra-VMPO microinjection of the NO donor sodium nitroprusside (5 µg) reduced Tc. The antipyretic effect of NO is likely to be mediated by activation of soluble guanylate cyclase and consequent rise in cGMP levels since: 1. NO is known to activate soluble guanylate cyclase; 2. intra-VMPO microinjection of the cGMP analogue 8-Br-cGMP reduced Tc similarly to the NO donor; and 3. the changes in AV3V levels of Nitrite/Nitrate and cGMP were similar in the course of fever. Surprisingly, we observed that Nitrite/Nitrate and cGMP levels decreased in the AV3V after, but not before, the onset of LPS fever, showing that the activity of the NO-cGMP pathway is reduced in the AV3V after i.p. LPS, a mechanism which could contribute to the genesis and maintenance of fever. Therefore, we suggest that the latency for the onset of fever is determined not only by the time that peripherally generated pyrogens signal the brain, as usually thought, but also seems to be under the control of antipyretic pathways. It was also observed that the efficacy of 8-Br-cGMP to reduce Tc in the VMPO is increased after LPS. This response could explain why intra-VMPO L-NMMA anticipated the onset of fever, even though the activity of the NO pathway before the onset of fever was similar to that of euthermic animals. In summary, these data support an antipyretic role of the NO-cGMP pathway in the VMPO, inhibition of which seems to contribute for the genesis of fever.

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## NEUROCHEMICAL CORRELATES OF HYPERTHERMIA-INDUCED BEHAVIOURAL CHANGES

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Extremes of environmental conditions such as cold, heat act like typical stresses that bring into play in the homeothermic animal a complex of biochemical, behavioural and physiological changes. Heat stroke is a common occurrence in certain parts of India, and in some other countries where the elevated temperature reaches the peak during the summer months. Heat stroke is characterised by disturbances of the central nervous system. Hyperpyrexia typically occurs when the environmental temperature is very high. Therefore the effect of exposure to elevated temperature of  $44^0\text{C}$  for 120 minutes in the rats on alterations in RNA, DNA, Total protein, transaminases of the brain and behavioural alterations is studied in the albinorat, since the central nervous system is vulnerable to heat stroke with associated dysfunction. The animals whose rectal temperature ( $\text{Tr}$ ) reached above  $42^0\text{C}$  only were included in this study. Thermal-stress affected animals showed a reduction of nucleic acids with alterations in the transaminases. These changes were correlated with hyperthermia induced cerebral derangement, and the characteristic behavioural changes. Sensitivity of brain tissue to hyperthermia is higher than that of other tissues. Changes in personality and behaviour such as aggressive behaviour, apathy and impaired arousal occur during heat exhaustion above  $39-39.5^0\text{C}$ , and several workers emphasised the existence of temperature gradients within the body. Thermal stress-induced neurochemical alterations reported in this study indicate cellular degeneration. Thermal stress also induced elevation of rectal temperature and the animals exhibited decreased locomotor activity and assumed sleeping posture. This is synonymous with heat stroke effects in humans, who showed characteristic behavioural changes, including reduced movement, a vivid interest in the environment and marked loquacity.

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## CENTRAL IMIDAZOLINE AND ANGIOTENSIN II RECEPTORS IN CARDIOVASCULAR RESPONSES TO CHRONIC COLD EXPOSURE IN RATS

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Clinical observation and epidemiological survey have proved that people living and working in cold areas have a high incidence of hypertension and related cardiovascular diseases. Cold winter weather makes hypertension severer and induces myocardial infarction and stroke in hypertensive patients. Thus, it is important to understand the mechanism underlying cardiovascular responses to chronic cold exposure. Our previous studies have shown that chronic exposure of rats to mild cold (5°C) induces hypertension and cardiac hypertrophy. It has been reported that central imidazoline (I<sub>1</sub>) receptors play an important role in cardiovascular responses to environmental stimuli. The objective of this experiment is to determine whether activation of central I<sub>1</sub> receptors affects the development of cold-induced hypertension (CIH). Four groups (7/each) of Harlan Sprague-Dawley rats were used. Blood pressures (BP) of all groups were similar during the control period. Two groups were exposed to cold (41°F; 5°C), while the remaining groups kept at 25 °C. One cold-exposed (CE) and 1 warm-adapted (WA) group were treated chronically, via osmotic minipumps, with an I<sub>1</sub>-receptor agonist, rilmenidine (R; in artificial CSF, 30 µg/hr, icv) and a specific  $\alpha_2$ -receptor blocker, SK&F-86466 (5 µg/hr, icv). The remaining groups received CSF only and served as controls. The implantation of minipumps were carried out under anesthesia (sodium pentobarbital 35 mg/kg, ip). The treatment lasted for 4 weeks. BP of the CE control group increased significantly during the first week of exposure to cold and rose to 162±5 mmHg by the 4th week, while BP of the CE, R-treated group did not increase and remained at the WA control level (118±3 mmHg). Withdrawal of R resulted in an increase in BP to the level of the CE controls at the 8th week of exposure to cold. Plasma renin activity and urine norepinephrine output were significantly decreased in the CE, R-treated group during the 4th week, suggesting inhibition of sympathetic nervous system and renin-angiotensin system. Pressor response to icv angiotensin II (AII) was significantly increased in the CE control group. However, AII-induced presor response was absent in the CE, R-treated rats at the 4th week, indicating that AII-induced presor effect was inhibited by activation of I<sub>1</sub> receptors. Inhibition of pressor response to AII disappeared at the 8th week upon withdrawal of R at the end of the 4th week. Thus, it is concluded that activation of central I<sub>1</sub> receptors could prevent the development of CIH and this may be related to inhibition of pressor effect of central AII. This finding also reveals possible relationship between central AII and I<sub>1</sub> receptors in cardiovascular responses to chronic cold exposure.

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## **THERMAL AND NUTRITIONAL STATUS AND THE DEVELOPMENT OF POSTNATAL RISE IN MINIMUM METABOLIC RATE OF THE RABBIT**

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In the process of transition from intrauterine to extrauterine life, resting metabolic rate (RMR) is known to increase postnatally. The mechanism of this adaptation phenomenon is not known; it can be connected probably to the changing conditions, mainly to the change in thermal environment (for cold extrauterine environment) and to the change in nutrition (for enteral nutrition). In the present studies the effects of environmental temperature and feeding status on postnatal metabolic rate were analyzed. RMR values of 72 newborn New Zealand White rabbit pups were measured on a total of 149 test occasions. At tests the pups belonged to one of the following age groups: 0-6-h, >6-12-h, >12-36-h, >36-72-h, >72-120-h and >120-168-h. Between tests the pups were (with some exceptions) returned to the maternal nest, which was relatively cold and in which feeding started relatively late (usually by the end of the first postnatal day, with great variability). Feeding status was judged by appearance of the pups and by their weight gain in the course of increasing postnatal age. At tests, the pups were placed into an open-circuit metabolic chamber immersed in a water-bath, which was warmed from 23-25 °C by a rate of 1°C/10min. During this warming, colonic temperature was measured by thermocouples, metabolic rate by diaferometer. Metabolic rate was expressed on body mass basis. The lowest metabolic rate observed in this process was regarded RMR, provided the animal was quiet. No RMR change was observed between the first 2 age groups. However, by the age of >12-36-h RMR exhibited a 27% rise, irrespective whether the animals were fed or unfed. A group of 9 pups was not returned to the doe after test at age 0-6-h, they were transferred to an artificial nest in a thermostat of 35-36°C (thermoneutrality). Pups of this group were unexposed to cold, and they exhibited no significant RMR rise by the age of >12-36-h (afterwards they were not returned to the doe, they had a narcotic overdose). In case the pups were not fed even beyond the age of 36-h, they could not sustain the high RMR. In 6 such fasting pups RMR had risen by the age of >12-36-h, but declined to the immediate postnatal level by the age of >36-72-h. In contrast, 7 pups, unfed at the age of >36-72-h were successfully fed later, by the age of >72-120-h their weight gain was 31% and their RMR rose to the level seen in normally fed pups of the same age. This is remarkable, since the consumed milk was not yet absorbed and incorporated into metabolically active body mass. It is concluded that 1) In the rabbit, cold exposure is necessary for the early postnatal rise in RMR, while the feeding status has no role in the development of this rise. This RMR-rise is thought to be connected with cold-induced changes of thyroid functions. 2) The high RMR cannot be sustained without onset of enteral nutrition. Fasting leads to a decline of the already high RMR. 3) Late-onset feeding of previously fasting pups results in large increase of RMR (per body mass, including gastric content), despite the still low active body mass. This RMR-rise may be connected with stretch and other gastrointestinal signals.

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## THERMOREGULATORY "OVERSHOOT" REACTIONS IN COLD-ADAPTED RATS

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Cold-adapted (CA) rats, as compared with non-adapted (NA) ones, have been reported to give enhanced metabolic response to acute cold exposure (Székely *et al.*, 1994). This may be due to altered function of thermosensors (Székely and Mercer, 1999), to altered central processing of thermoregulatory information, or to altered metabolic responsiveness of tissues. In the present studies the possibility of cold adaptation-induced regulatory changes was checked. Wistar rats were adapted to a room of 3-5 °C or 22-25 °C (CA or NA group, respectively). Temperatures of the colon ( $T_c$ ), tail skin ( $T_s$ ), and metabolic rate (MR) of CA vs. NA rats were analyzed at 25 vs. 30 °C (thermoneutrality) and after exposure to moderate (15 vs. 21 °C) or to intense (5 vs. 15 °C) cold. Temperatures were measured by thermocouples, MR by diaferometer, while the rats stayed semirestrained in a metabolic chamber. Resting MR at thermoneutrality is higher ( $8.10 \pm 0.32$  W/kg),  $T_c$  is lower ( $37.84 \pm 0.05$  °C) in CA rats (as compared with  $6.05 \pm 0.23$  W/kg and  $38.33 \pm 0.09$  °C, respectively, in NA rats); the high MR is counterbalanced by earlier onset of cutaneous heat loss. Acute cold exposure causes an immediate MR-rise, without initial  $T_c$ -fall in CA rats; this MR rise exceeds the actual need („overshoot”) and results in „paradoxical” elevation of  $T_c$  (persisting as long as the cold exposure); upon re-warming both MR and  $T_c$  fall. Comparable cold exposure in NA rats (e.g. similar MR rise in % in NA rats exposed to 15 °C and CA rats exposed to 5 °C, or similar MR level in NA and CA rats at 15 °C) always causes  $T_c$ -decline and slow MR-rise, in sharp contrast to CA rats. Stepwise cooling of CA rats causes stepwise rise in  $T_c$ , suggesting that the overshoot MR- and  $T_c$ -levels are not due to the rate of cooling, rather to the actual severity of cold which alters the regulated levels of MR and  $T_c$ . It is concluded that oversensitive peripheral cold sensors, while stimulated, sustain a too high metabolic tone and a paradoxically high  $T_c$ . The high metabolic activity of tissues (e.g. brown fat) and the enhanced responsiveness of tissues to thermogenic (e.g. noradrenaline) stimuli contribute to the overshoot phenomenon. This phenomenon can still be explained basically by regulatory changes: increased cold sensitivity plus greater central regulatory responses (altered central processing of thermoregulatory information), resulting in greater outgoing signal to the peripheral heat producing/conserving mechanisms

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## ROLE OF THE MEDULLARY RAPHÉ NUCLEI IN THERMOREGULATORY VASOMOTOR CONTROL IN RATS

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The preoptic area plays a key role in body temperature regulation by integrating information about local brain temperature and other body temperatures, and by sending efferent signals to various effector organs. Recent findings suggest that the control of both heat production and heat loss are regulated mainly by signals from warm-sensitive neurones rather than those emanating from cold-sensitive neurones. That is, warm-sensitive neurones in the preoptic area send excitatory efferent signals for heat loss, and inhibitory signals for heat production. In rats non-evaporative heat loss occurs mainly through the tail skin, and is controlled by the sympathetic vasoconstrictor nerve. Recent studies suggest that the medullary raphé nuclei may play an important role in the cutaneous vasomotor control. We investigated the role of the medullary raphé in the thermoregulatory vasomotor control, and its connections with the preoptic area. Each of adult male specific pathogen-free crj-Wister rats (290–400 g) was anaesthetized with urethane (1.4 g/kg, i.p.). For preoptic warming, an electrode-thermocouple assembly was implanted into the preoptic area, and for drug application a cannula was inserted into the medullary raphé. A polyethylene catheter (filled with heparin saline, 50 U/ml) was implanted in the right femoral artery to monitor arterial blood pressure and heart rate. Vasodilation occurred in response to preoptic warming. When an excitatory amino acid, D,L-homocysteic acid (DLH:0.5 mM, 0.3 µl) was injected in the raphé nuclei during preoptic warming, vasodilation was transiently suppressed, which often accompanied with increase in blood pressure. The effective sites were restricted in the caudal part of the raphé nuclei. When GABA<sub>A</sub> receptor antagonist, bicuculline (500 µM, 0.3 µl) was injected into the DLH-effective sites, vasodilation did not occur even though the preoptic area was warmed. Finally, we injected a retrograde tracer, cholera toxin B (CTb) into the caudal part of the raphé nuclei. A large number of cells were labelled with CTb in the preoptic area and in the midbrain periaqueductal grey (PAG), where tail vasodilation is produced by electrical/chemical stimulation (Zhang *et al.* 1997). These results suggest that vasoconstrictive neurones exit in the caudal part of the medullary raphé nuclei, and they receive inhibitory signals from the preoptic area, which would be responsible for tail vasodilation by preoptic warming. But it is uncertain whether the signals from the preoptic area are directly transmitted to the medullary raphé nuclei or via the PAG.

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## OXYGEN CONSUMPTION AND HEART RATE RESPONSES TO LOWERED AMBIENT TEMPERATURES IN CHICK EMBRYOS AND HATCHLINGS

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The domestic fowl (*Gallus gallus domesticus*, referred to as chick) is precocial species and embryos hatch after about 21 days of incubation at 38°C. Gas exchange is made by molecular diffusion through the chorioallantoic membrane (CAM) and porous eggshell prior to internal pipping (i.e., pipping internally the CAM; IP). With initiation of lung breathing, both the diffusive and convective gas exchanges by the CAM and lungs are made in the egg with subsequent increase in the latter during external pipping (i.e., pipping externally the eggshell). The incubation period prior to initiation of IP on days 19-20 is referred to as prenatal period and the embryo, the prenatal embryo. The period beginning with IP and ending up hatching is referred to as perinatal period of incubation and the embryo, the perinatal embryo. The perinatal period after hatching may be designated as postnatal period and the chick, hatchling or newly hatched chick. In order to investigate the development of thermoregulatory capacity in the prenatal and perinatal chick embryos, we previously developed two cooling tests which examined oxygen consumption responses of the embryo to lowered ambient temperature exposures. One was a gradual cooling test and another was a prolonged cooling test. Both tests were made by keeping the imbalance between heat loss from the egg and heat production of the embryo as small as possible while the egg was cooling and oxygen consumption was measured. The incipient compensatory increases in oxygen consumption were found in perinatal chick embryos. The perinatal embryos needed not emerge from the egg for the compensation to occur. We suggested general model of the development of homeothermy in precocial and also altricial birds (Tazawa et al., 1988; Whitow & Tazawa, 1991). In addition to these reviews, in the present report we investigated the heart rate responses of perinatal chick embryos and postnatal hatchlings to lowered ambient temperature exposures. The instantaneous heart rate (IHR) was determined from ECG measured by specially designed silver wire electrodes in perinatal embryos inside the eggshell and by flexible disk electrodes in hatchlings. Some externally pipped (EP) embryos failed to hatch on day 22 of incubation and stayed inside the eggshell for more than 1-2 days. These EP embryos responded to low temperature exposures by raising the IHR baseline and in addition the raised baseline HR began to oscillate with a period of 10-20 sec. These trends were more dominant in hatchlings. Particularly, in hatchlings, the HR oscillations which appeared in a low temperature environment disappeared when they were warmed. Thus, the HR oscillations with a period of 10-20 sec which often occur in developing hatchlings are distinctive evidence related to thermoregulation of hatchlings.

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## MEASUREMENT OF BODY SURFACE AREA USING 3D LASER SCANS

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3D laser scanning technology and sophisticated graphics editing software were applied to determine human body surface area (BSA). Whole-body scans of 641 adults (395 males and 246 females) were obtained from the anthropometric data base of the Civilian American and European Surface Anthropometry Resource project. BSA was calculated after detailed surface editing of the scans that involved patching and smoothing to produce closed surfaces. 12 males and 12 females (G24) were chosen from the entire population for detailed measurements of the surface area of the hand ( $SA_{hand}$ ) and of the ratios of the surface area to volume (SA/VOL) of various body segments. Regression formulae involving wrist circumference and arm length were subsequently used to predict  $SA_{hand}$  for the remaining population. Overall mean  $\pm$  SD of BSA were  $2.03 \pm 0.19$  and  $1.73 \pm 0.19 \text{ m}^2$  for men and women, respectively. Various published prediction formulae were then compared and although most predicted close to the BSA measured herein, residual analysis revealed in most cases an overprediction with increasing body size. Non-linear regressions were performed for each gender separately and these yielded the following best-fit formulae (with root mean square errors of  $\sim 1.3\%$ ):  $BSA(\text{cm}^2) = 128.1 \cdot WT^{0.44} \cdot HT^{0.60}$  for men and  $147.4 \cdot WT^{0.47} \cdot HT^{0.55}$  for women, where WT is in kg and HT is in cm. The SA/VOL ratio of various body segments were higher for the females compared to the males of G24, significantly for the head plus neck (by 7%), torso (19%), upper arms (15%), forearms (20%), hands (18%), and feet (11%). The SA/VOL ratios for both genders ranged from  $\sim 12 \text{ m}^{-1}$  for the pelvic region to  $104 - 123 \text{ m}^{-1}$  for the hands.

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## COMPARISON OF PHYSIOLOGIC AND PERCEPTION BASED INDICES OF HEAT STRAIN

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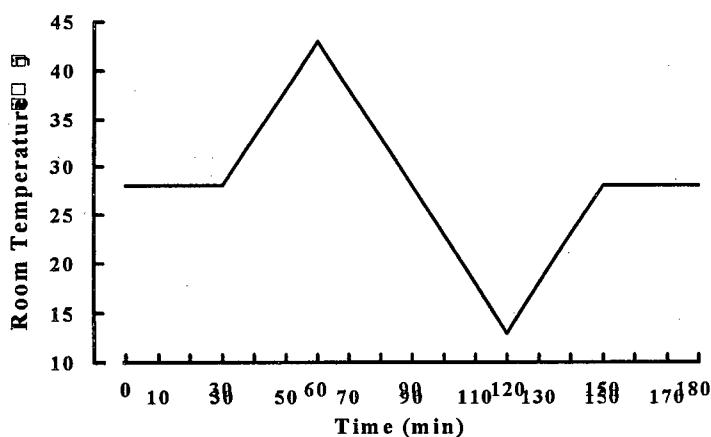
The physiological strain index (PSI) has recently been introduced as a universally-applicable measure of the strain induced by exercise-heat stress. PSI (on a scale of 0 to 10) gives equal weight to normalized increases in deep body temperature ( $T_c$ ) and heart rate. However, PSI has not been compared to an index modelled by the perception of these physiological changes. Following the same mathematical recipe as the PSI, the perceptions of thermal sensation and perceived exertion were combined and the resultant index, PeSI, was then compared to its physiological counterpart. Twenty males and six females participated in an exercise-heat stress experiment for this purpose. Subjects were grouped according to their level of aerobic fitness [athletically trained (T) and untrained (U)]. U subjects ( $n = 13$ ) had a higher level of body fatness (mean  $\pm$  SD  $18.1 \pm 5.3$  vs.  $12.6 \pm 4.5\%$ ;  $p < 0.010$ ) and a lower level of aerobic fitness ( $VO_{2\text{max}} = 43.6 \pm 3.8 \pm$  vs.  $59.0 \pm 6.2 \text{ mL}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ ;  $p < 0.001$ ). While wearing semi-impermeable clothing, subjects walked ( $3.5 \text{ km}\cdot\text{h}^{-1}$ ) under hot conditions ( $40^\circ\text{C}$  and 30% RH) until exhaustion or when their  $T_c$  reached  $39.5^\circ\text{C}$ . There was no group difference in PSI, yet T perceived their physiological strain lower than U ( $p < 0.002$ ) during the first 60 min of exposure. There was also no difference between the indices for U whereas PSI was higher than PeSI for T ( $p < 0.008$ ). By the end of the exposure ( $69.2 \pm 11.5$  vs.  $94.6 \pm 17.7$  min for U and T, respectively;  $p < 0.001$ ), T had a higher value of PSI ( $8.23 \pm 0.72$  vs.  $6.74 \pm 1.47$ ;  $p < 0.002$ ) but there was no group difference in PeSI. While the indices were not different for U, PSI was higher at the end than PeSI for T ( $6.14 \pm 1.68$ ;  $p < 0.001$ ). Thus, T underestimated their PSI throughout the exposure whereas U consistently perceived their physiological strain in accordance with the measured increases in core temperature and heart rate.

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## THERMOREGULATORY AND CARDIOVASCULAR RESPONSES OF YOUNG AND ELDERLY MEN TO AIR TEMPERATURE CHANGE

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The purpose of this study was to investigate the effect of room temperature change on physiological and subjective responses in the elderly and the young. The subjects were all healthy, medically-screened volunteers: 9 young men (mean age 22.3 years) and 9 older men (mean age 69.6 years). They wore only shorts during the experiment. Ambient temperature (Ta) of the climatic chamber was set at 28 °C for 30 min. The Ta increased linearly to 43°C 30 min later, and decreased to 13°C 60 min after that. From 13°C the Ta moved to 28°C in 30 min and remained there for 30 min more as shown in the Figure below. Rectal temperature(Tre), skin temperatures at 10 points, blood flow and sweat rate were measured continuously during the three hour experiment. Heart rate (HR), blood pressure, thermal sensation and thermal discomfort were measured every 10 min. The experiments were carried out in summer. Average Tre of both groups were almost the same for 120 min, however, when the Tre of the elderly decreased more deeply at the end of the experiment, the difference between the groups became significant. As shown by hand skin temperature, the elderly could not reduce heat loss by vasoconstriction as could the young. HR in the young during the heat exposure was significantly higher than in the elderly, but there were no significant differences in HR between the groups during the cold exposure and the second 28°C period. On the other hand, systolic blood pressure (SBP) was similar in both groups during the first 28°C period and during heat exposure, but during the cold exposure SBP in the elderly were significantly higher than in the young. These differences in SBP continued even when Ta increased. Although the elderly subjects had less vasoconstriction in their extremities, due to the decreased sensitivity of their baroreceptor reflexes, SBP increased more during cold exposure than in the young. The elderly's lower core temperature probably caused their much higher blood pressure in the latter part of the experiment. There were no differences in thermal sensations between the groups during the experiments, but the degree of thermal discomfort for the elderly during heat and cold exposures were significantly smaller than for the young. Physiological after effects from cold exposure were more marked for the elderly, but they seemed less aware of them than the young.



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## CATECHOLAMINES AND CORTISOL IN THERMOREGULATION OF CHICKEN AND DUCK EMBRYOS INCUBATED UNDER LOWERED TEMPERATURE

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During the embryological development the nerval and the hormonal regulatory system has to be developed to a stage, that they are able to adapt the organism from prenatal protected life to the completely different as well as changing environmental conditions. The prenatal mammal in the uterus is protected against various exogenic influences by the mother. In comparison to that the avian embryo has to react very early to stress factors with own regulatory systems. The sympato-adrenal system plays a pivotal role in the adaptation of body to stress by providing an immediate response to any stressor. The main function of the Catecholamines (CA): noradrenaline-NA, adrenaline-A and dopamine-DA is to protect the embryo from deleterious hypoxic damages in the end of embryogenesis by improving the blood gas status and the redistribution of cardiac output in favour of heart, brain and chorioallantoic membrane. When respiration changes from the chorioallantoic circuit to the lungs, Corticosteroids stimulate the synthesis of surfactant and Cortisol (C) is responsible for glucose metabolism. Under the condition of stress, C permits a permissive effect to CA by an increasing sensitivity to the CA-receptors in circuit. All these functions of hormones support the possibility of thermoregulation. Our basic question was whether lower prenatal temperatures for certain periods of time had any influence on CA and C in plasma of the chick embryo in comparison with duck embryo. The present study aimed at the influence of two temperatures (37.5°C and 35.0°C) on the CA- and C-concentrations in plasma of chick and duck embryos. The incubation temperature was decreased (35.0°C) at day of incubation (D)14 for chicken embryos and at D23 for duck embryos. The control group was continuously incubated at 37.5°C. The day on which the incubation temperature was changed in the duck is determined in relation to the chicken embryo's age. D14 of the chicken and D23 of the duck are equivalent to 66% of their respective incubation time. CA were determined by HPLC, C with testkits (Sigma-Aldrich). The Table shows the median of hormone concentrations (ng/ml) in chick and duck embryos from selected incubation days.

	Chicken						Duck					
	D18		D19		D20		D30		D31		D32	
T [°C]	37.5	35.0	37.5	35.0	37.5	35.0	37.5	35.0	37.5	35.0	37.5	35.0
DA	6.9	7.3	5.9	7.4	10.5	9.8	1.8	1.3	1.6	1.2	2.2	1.9
NA	13.3	13.6	21.9	8.2	38.5	15.6	17.6	9.3	26.6	9.6	11.9	33.6
A	1.8	0.5	5.9	0.5	11.2	0.9	4.7	0.9	4.1	1.6	3.2	5.4
C	3.1	2.7	4.3	5.6	5.4	4.6	5.8	5.2	7.9	7.0	7.4	8.5

In chick embryos we found an age dependent increase in hormone levels at 37.5°C and at 35.0°C from D18 to D20. In duck embryos an increase was found between D30 to D32 only at 35.0°C. The longer – term decrease of incubation temperature influenced the CA- and C-concentration in plasma. Considering the physiological function of these hormones in chicken and duck embryos- the influence on metabolism and circuit – thermoregulation can be assumed at 35.0°C in both.

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## THE EARLY DEVELOPMENT OF NEURONAL HYPOTHALAMIC THERMOSENSITIVITY IS INFLUENCED BY EPIGENETIC TEMPERATURE ADAPTATION

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During embryonic development, changes in environmental conditions induce alterations in postnatal development of control systems like the thermoregulatory system. Birds incubated at lower or higher temperatures than usual were postnatal cold or warm adapted. In our own experiments in ducklings, for instance, heat production was higher (56%) in cold-incubated birds (34.5°C) than in normally incubated ones under cold load (10°C) on the first day after hatching. Besides this, cold-incubated ducklings prefer lower ambient temperatures during the first 10 days post-hatching than birds incubated at the usual 37.5°C. Obviously, these alterations are the result of epigenetic adaptation processes. It is to assume, that in the brain epigenetic adaptation processes results in a changed neuronal activity. In relation to that, in our experiments we investigated the prenatal influence of different incubation temperatures on the development of central neural thermoregulatory mechanisms in ducklings. Experiments were carried out in 1-, 5- and 10-d-old Muscovy ducklings (*Cairina moschata*) incubated at 35°C, 37.5°C (control) and 38.5°C during the last week of incubation. At the day of the experiments the birds were decapitated and the brain removed. 400 µm thick brain slices including the preoptic area of the anterior hypothalamus (PO/AH) were prepared. Using the method of extracellular recordings, neuronal thermosensitivity of PO/AH neurons after sinusoidal temperature changes (40°C ± 3°C) was investigated. The proportion of cold- (C) and warm-sensitive (W) and temperature-insensitive PO/AH neurons was determined in all age groups, investigated. The results show, that changes in incubation temperature induced a clear alteration of neuronal hypothalamic thermosensitivity during the first 10 days post-hatching, but this alteration was independent (proximate nonadaptive) of the direction of changes in incubation temperature between day 1 and 5. In 1- and 5-d-old ducklings the proximate nonadaptive change in neuronal hypothalamic thermosensitivity after different prenatal temperature load might be typical for this early stage of ontogeny. Proximate nonadaptive alterations to various exogenous factors were also found in many body functions (e.g. blood flow of the allantoic membrane, heart rate) during early development in birds as well as in mammals. On the 10th day post-hatching prenatal temperature experiences induced an incubation temperature dependent alteration of the thermosensitivity of PO/AH neurons (proximate adaptive). In 10-d-old birds cold load elevated hypothalamic warm-sensitivity through an increased proportion of W-neurons and a reduced proportion of C-neurons. Prenatal warm load induced an opposite effect. We conclude, that in differently incubated birds the observed alteration in the activity of PO/AH neurons which results in changes in neuronal thermosensitivity of the thermoregulatory center is caused by epigenetic adaptation processes.

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## ENHANCED RESPONSIVENESS TO CENTRAL PROSTAGLANDIN E OR NEUROPEPTIDE Y IN COLD-ADAPTED RATS

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In contrast to non-adapted (NA) rats, cold-adapted (CA) rats give "overshoot" rise in metabolic rate (MR) upon acute cold exposure (Székely *et al.*, 2001). This might be explained by an enhanced sensitivity of peripheral temperature (cold) sensors (Székely and Mercer, 1999), possibly by high tissue thermogenesis and increased tissue responsiveness to thermogenic stimuli, but might also be explained by altered central processing of thermoregulatory information. Now this last possibility was analyzed and the effects of non-thermal influences on central regulatory functions were studied. Wistar rats were accustomed to handling and body weight measurements. They were adapted to a room of 22-25 or 3-5°C (NA or CA groups) temperature, with lights on between 6.00-18.00 h. Under intraperitoneal ketamine + xylazine (78 + 13 mg/kg) anesthesia guide-cannula was implanted into a lateral cerebral ventricle (i.c.v.). One week later the rats were semi-restrained, placed in a metabolic chamber and 100 ng prostaglandin E<sub>1</sub> (PGE, Sigma) was injected i.c.v. at thermoneutrality (25°C for CA, 30°C for NA rats). Metabolic rate (MR) and colonic temperature (T<sub>c</sub>) were measured by diaferometer and thermocouples, respectively. Similar measurements were done after i.c.v. injection of 10 µg neuropeptide Y (NPY, Bachem) at cool (15°C for CA, 20°C for NA) or thermoneutral temperatures. In other cases, cumulative body weight changes, as indicators of food intake (FI) were measured for 3-h following i.c.v. injection of 2 µg NPY at 9.00 at the adaptation temperature (or in some CA rats at 22-25°C), while the rats stayed in their home-cages where chow and water were freely available. After the experiments the rats were given a narcotic overdose. Resting MR was higher, T<sub>c</sub> was lower in CA than in NA rats. Both MR and T<sub>c</sub> rose following PGE (but not saline) injections; the rises were significantly greater in CA rats. In cool environments NPY induced slightly more pronounced T<sub>c</sub>-fall in CA than in NA rats. NPY induced FI in both groups, but the response was significantly greater in the CA group. 0.9% NaCl injections were without effect on FI. The actual environmental temperature at which the food was offered did not influence the FI response of CA rats to NPY. It is concluded that CA rats, similarly to their "overshoot" thermoregulatory response to peripheral cold, are hyper-responsive to direct central stimuli, without any change in peripheral thermal signals. Identical PGE amounts evoke greater thermoregulatory responses in CA animals. This is not due to increased thermogenic capacity of peripheral tissues, since similar phenomenon can be shown for NPY in FI regulation. Apparently, central regulatory responsiveness is generally enhanced in CA rats.

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## EFFECT OF MILD COLD ON METABOLIC AND INSULATIVE ADAPTATION IN MAN

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Some studies show that exposure to mild cold causes an increase in temperature gradient (core-skin), while other studies show that energy metabolism increased. The relative contribution of each form of adaptation during mild cold has not been studied. Therefore we studied the short-term effect of mild decrease in environmental temperature on energy metabolism and body temperature distribution. 9 Males stayed 2 consecutive days at 16 °C and one day at 22 °C in a respiration chamber. 24 h EE, diet induced thermogenesis (DIT), sleeping metabolic rate (SMR), activity induced energy expenditure (AEE), and rectal and skin temperatures were measured.

Proximal skin temperatures were 1.2±0.8 °C lower at 16 °C compared to 22 °C, while distally the difference was 4.8±1.6 °C. At 16 °C body core temperature was significantly 0.2±0.15 °C lower than at 22 °C (p<0.01). Temperature gradients increased significantly at 16 °C compared to 22 °C (p<0.01). At 16 °C 24 h EE, DIT and AEE increased compared to 22 °C (p<0.02, P<0.005, p<0.05, respectively). In search for acclimation effects day 1 and day 2 at 16 °C were compared. 24 h EE and AEE were elevated on day 2 compared to day 1 (p<0.02 and p<0.05). No apparent significant differences in body temperatures were found. However, the change in body temperature gradients (core-proximal skin) was negatively related to the change in 24 h EE ( $R^2=0.82$ , p<0.002). This means that those subjects with little or no increase in 24 h EE showed an increase or no change in their body temperature gradient, while those that increased their 24 h EE showed a decrease in their body temperature gradient.

The results show that inter-individual differences exist with respect to the relative contribution of metabolic and insulative adaptations to mild cold.

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## A MATHEMATICAL MODEL OF THE DYNAMIC THERMAL INTERACTIONS BETWEEN CLOTHING AND HUMAN THERMOREGULATORY SYSTEM

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This paper presents a mathematical model that simulates the dynamic thermal interactions between clothing materials and the human thermoregulatory system, which is solved by finite difference method. The model consists of two parts: a clothing heat and moisture transfer model and a thermoregulatory model of the human body. The clothing heat and moisture transfer model is a mathematical model that describes the heat transfer processes by conduction and radiation and the moisture transfer processes by diffusion, fiber moisture sorption. Condensation/evaporation, and capillary actions, as well as the coupling effects among them are considered. With specification of boundary conditions of the temperature and humidity at the clothing-skin and clothing-environment interfaces, the dynamic changes of the distribution of the temperature, moisture contents and the volumetric fraction of the liquid water throughout the fabric are calculated. For describing the thermoregulatory responses of the human body, Gagge's two-node thermoregulatory model is used, which takes into account of the passive heat balance and transfer processes and the moisture transfer processes in the body, and the thermoregulatory controlling mechanisms of heat production, sweating and blood flow. By interfacing these two models, we developed a mathematical model that is able to simulate the dynamic thermal interactions between clothing and the body thermoregulatory system, particularly in the transient conditions. Using this model, we are able to illustrate mathematically how the clothing materials influence the thermoregulatory responses of the body such as sweating rate, blood flow, heat production by shivering, body core temperature and skin temperature profiles, as well as temperature and moisture profiles in the clothing during the transient changes of environment and/or physical activities. By changing the various combination of thermal status of human body, clothing material and environmental conditions, the model can be used to study the physiological thermal responses and comfort status of the human body such as heat stresses and cold stresses under various transient conditions.

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## A MINI-REVIEW ON THE ROLE OF ANGIOTENSIN II AND ITS RECEPTORS IN THE DEVELOPMENT OF FEVER IN RODENTS

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Angiotensin II (ANG II) has recently been recognized as one of the stress hormones that participate in various stress-induced responses, including hyperthermic response. Fever may be one of the stresses (i.e., immunological stress), because the stimuli that induce fever stimulate the hypothalamo-pituitary-adrenocortical axis and sympathetic nervous system. Recent studies have revealed the existence of two types of ANG II receptors in the brain, AT<sub>1</sub> and AT<sub>2</sub>. In this mini-review, we summarize our findings on the role of ANG II and its receptors in the development of fever in rodents. We report an inhibition by intrahypothalamic (i.h.) injection of AT<sub>2</sub> receptor antagonist (5 µg) of the fever induced in rats by intraperitoneal (i.p.) injection of interleukin-1 (IL-1, 2 µg/kg) or i.h. prostaglandin E (PGE, 100 ng). The PGE-induced fever in rats was enhanced by treatment with ANG II (25 ng, i.h.) but was reduced by angiotensin converting enzyme (ACE) inhibitor (10 µg, i.h.). ANG II alone had no effect on the resting body temperature. Moreover, we present our results showing an attenuation of IL-1 (10 µg/kg, i.p.)-induced fever in the AT<sub>2</sub> receptor-deficient mice. It is, therefore, likely that AT<sub>2</sub>-receptors contribute to the fever induction in mice as well as in rats, and that hypothalamic AT<sub>2</sub>-receptors modulate the PGE fever in a positive way at the final step of fever induction. On the other hand, we present in this mini-review our very recent results showing that the fever induced in dehydrated rats by intravenous (i.v.) injection of lipopolysaccharide (LPS, 2 µg/kg) was attenuated by systemic administration of ACE inhibitor (10 mg/kg, i.v.), while the fever induced by IL-1 (2 µg/kg, i.v.) was not. These results suggest that ANG II is involved in the development of fever induced in dehydrated rats by i.v. injection of LPS via stimulating the production of pyrogenic cytokines, such as IL-1. Taken together, it is likely that ANG II and AT<sub>2</sub> receptors contribute to the induction of fever at the final step by affecting the processes mediated by PGE, and that ANG II participates, at the first step of fever induction, in the synthesis and release of pyrogenic cytokines in response to LPS.

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## **IMPACT OF TOXIC AGENTS OR ADVERSE CONDITIONS ON THERMOREGULATORY FUNCTION IN AWAKE RODENTS**

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In response to exposure to xenobiotic agents, rodents demonstrate significant acute and subchronic decreases in important indices of thermoregulatory and cardiovascular function (termed the *hypothermic response* (Watkinson & Gordon, 1993)). These effects are often accompanied by similar decreases in related parameters (e.g., metabolic rate, cardiac output, respiratory rate) and may predispose treated animals to adverse arrhythmic events and lethaliities. This response has been observed in a number of studies in our laboratory and appears remarkably consistent, despite the variety of agents (anesthetics, pesticides, ozone, particulate matter, metals, others) and exposure routes (intravenous, intraperitoneal, intratracheal instillation, inhaled) tested. Furthermore, these effects may be modulated by seemingly routine changes in experimental conditions, and are especially sensitive to changes in ambient temperature ( $T_a$ ) and animal mass. For the most part, these studies used rats that were anesthetized with sodium pentobarbital (50 mg/kg; ip) and implanted with radiotelemetry transmitters capable of monitoring electrocardiogram, heart rate (HR), and core body temperature ( $T_{co}$ ); at least 7 days were allowed for recovery from these procedures before exposures were conducted. In initial studies, rats exposed to the pesticide chlordimeform (5-60 mg/kg, ip) exhibited acute decreases in  $T_{co}$  and HR of approximately 1.0-2.0°C and 50-150 bpm, respectively. In subsequent studies, exposure to ozone (0.5 ppm, inhaled) induced similar decreases in rats maintained at an  $T_a$  of 22°C. When the protocol for these ozone studies was repeated at an  $T_a$  of 10°C, decreases in  $T_{co}$  and HR averaged 2.5-4.0°C and 150-200 bpm, respectively. In similar studies in which mice were acutely exposed to ozone (2.0 ppm, inhaled),  $T_{co}$  deficits as high as 10°C were observed. Current studies involving both intratracheal and inhalation exposures of rats to particulate matter and its metallic constituents also induce  $T_{co}$  and HR decreases in the ranges of 1.5-3.0°C and 50-150 bpm, respectively, depending on the specific experimental conditions and animal models employed. In companion studies, biochemical indices of pulmonary injury have been shown to correlate well with the magnitudes of these responses. While the underlying mechanism/s remains undetermined, these effects have both physiological and behavioral components and appear to be mediated, in part, via the parasympathetic nervous system. Interestingly, unless severely stressed, humans do not appear to demonstrate this response. Thus, given that rats and mice represent the overwhelming majority of animal species used in toxicological testing, such effects may have important implications with respect to the interpretation and extrapolation of the results obtained from standard toxicological studies.

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Abstract does not represent US EPA policy.

## NEW TECHNIQUES FOR THE THERMAL PHYSIOLOGIST: USING CLINICAL

### MAGNETIC RESONANCE METHODS IN BASIC RESEARCH

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Magnetic resonance imaging (MRI) has become a powerful tool in non-invasive diagnosis of pathological and pathophysiological phenomena. Its main advantages are the use of non-ionizing radiation and the possibility to adjust the contrast of the images according to the tissues and phenomena involved. Imaging is disturbed by movements (body movements, respiration, blood flow) and by temperature changes. The latter effect may be converted into a measurement principle, if one remains aware that it will be highly disturbed by „imaging“, i. e. when measuring within different tissues and of course also by movements including perfusion. Basically, it is a technique delivering relative units, i. e. it has to be calibrated e. g. by fiberoptical measurements. Five techniques have been proposed and tested: Temperature dependence of 1. spin-lattice relaxation time („T<sub>1</sub>“), 2. Brownian motion (diffusion coefficient), 3. resonance frequency of protons, 4. equilibrium magnetization („M<sub>0</sub>“), 5. chemical shift of temperature sensitive complexes (lanthanides).

In contrast to the great number of studies on dead material, the successful application of temperature measurements in living organisms is still rather rare, mainly because of many additional problems. The measurements of T<sub>1</sub> *in vivo* proved to be difficult because it is disturbed by changes of proton density and of perfusion. One disadvantage of diffusion imaging is the anisotropy of the diffusion coefficient, meaning that the temperature dependence of the signal changes according to the direction of cells or fibers. Disadvantages of the use of lanthanide complexes include restricted spatial resolution and the invasiveness of the intravenous application of the agent. The proton resonance frequency method requires a complex image processing, including, like other methods, subtraction of different images. No detailed information seems to be available for the equilibrium magnetization methods. A common problem of most methods is the still long acquisition time, so that the requirement for no movement cannot be fulfilled. However, the development of fast MRI procedures and algorithms is an incredibly quick process which promises a continuous improvement. Nevertheless, at present, temperature measurement *in vivo* is not a routine procedure at all. Our lab focussed on temperature imaging of muscle, *in vitro* and *in vivo*, using spin-echo sequences making use both of the „T<sub>1</sub>“ and the „M<sub>0</sub>“-effect. The method proved to be less sensitive to motions than others with a high signal to noise ratio, the disadvantage still being the long acquisition time (about 5 min) and the interference with blood flow. If these drawbacks are of lower significance or can be overcome, an *in vivo* accuracy of less than 1 °C can be expected, together with a good spatial resolution. With further progress in this technology, there is no doubt that it will assist enormously in revealing some of the central secrets within the thermoregulatory system.

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## SEASONAL VARIATION IN BODY WEIGHT: AN EXPERIMENTAL CASE STUDY

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The effect of seasonal variation in ambient temperature on body weight was studied in one subject over three consecutive years (1997-2000), including a shift in the cold season to a tropic environment (1999). The subject was a man, 51 y, body mass index 21.7 kg/m<sup>2</sup>. Ambient temperature was a 24h average as monitored by the Royal Dutch Meteorological Institute at a location within 10 km. Body weight was measured daily, in the morning after getting up with an empty bladder and before any food or water intake, on a scale accurate to  $\pm 0.01$  kg. Ambient temperature ranged between a winter minimum of -3.4, -5.5 and -4.7 °C, and a summer maximum of 26.9, 25.8 and 24.4 °C over the three consecutive years. Body weight reached a winter maximum of 60.7, 60.7 and 60.3 kg, and a summer minimum of 57.4, 57.2 and 57.3 kg over the same interval. There was a strong negative correlation between body weight and ambient temperature ( $r^2 = 0.58$ ,  $p < 0.0001$ ), apart from the season with the shift from a low to a high ambient temperature. Then, body weight dropped from the winter value of 60.0 kg to 57.6 kg after two weeks in the tropics at 27 °C. Surprisingly, body weight remained at a similar value until the summer, despite ambient temperatures down to -4.7 °C in late winter. One of the potential mechanisms is a temperature induced rhythm in thyroid activity, where thyroid activity reduced after heat exposure in mid-winter to a summer low with a consequent reduction of body weight. In conclusion, body weight shows a clear seasonal variation triggered by ambient temperature, with a minimum in summer and a maximum in winter, possibly regulated by thyroid activity

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## CORE-SKIN GRADIENT OF BODY TEMPERATURE RELATED TO NON-SHIVERING

### THERMOGENESIS 3 IN HUMANS AT A LOWERED AMBIENT TEMPERATURE

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Energy expenditure (EE) is related to body temperature, and vice versa, while EE is related to ambient temperature as well. In a study in women, EE was higher at 22°C than at 27°C, 9.9 MJ/d versus 8.9 MJ/d ( $p<.001$ ), respectively (Westerterp-Plantenga et al 2001a). The difference was the result of an increase in diet induced energy expenditure (DEE,  $p<.01$ ) and of an increase in activity induced energy expenditure (AEE,  $p<.01$ ). At the same time, core ( $p<.05$ ), proximal (forehead, infra-clavicular zone) and distal (hand, foot, thigh) skin ( $p<.001$ ) temperatures had decreased. In a study in men, the increase in EE at 16°C compared to at 22°C, 12.9 MJ/d versus 12.2 MJ/d ( $p<.001$ ), consisted of increases in DEE ( $p<.01$ ) and in Sleeping Metabolic Rate (SMR,  $p<.05$ ), together with decreases in core, proximal and distal skin temperatures ( $p<.01$ ) (Westerterp-Plantenga et al. 2001b). Here, we addressed the effect of lowered ambient temperatures i.e. 22°C (72°F) vs 27°C (81°F) and 16°C (61°F) vs 22°C (72°F) on a part of 24h non shivering thermogenesis, named NST3, in the two referred studies. We define NST as the sum of NST1 (part of SMR), NST2 (part of DEE), and NST3 (part of resting EE or REE). In both studies, EE measured as DEE is in fact REE consisting of DEE and NST3. DEE is the acute effect of food ingestion on EE, which accounts for about 10 percent of EE. Relative DEE -as percentage of energy intake- normally should remain the same in comparable situations with respect to energy balance and macronutrient composition of the diet. Since the relative DEE appeared to be significantly different between the two different ambient temperatures within both groups of subjects, we considered this difference as being part of NST, named NST3. We hypothesized that NST3 contributes to the regulation of body temperature. NST3 was determined as total EE minus (SMR + DEE + AEE). Thus, NST3 was 248±208 kJ/d at 22°C and 714±505 kJ/d at 16°C, and was related to the core-skin body temperature gradient ( $r= -.95$ ,  $p<.001$ ; and  $r= -.7$ ,  $p<.05$ ; respectively). NST3 limited the increase in core-skin temperature gradient at a lower ambient temperature. NST1 was increased as well in the men at 16°C. We conclude that at a lower ambient temperature, the larger NST3, the smaller the core-skin body temperature gradient, i.e. the larger the area in which the decrease of body temperature is limited. Thus NST3 contributed indeed to the maintenance of body temperature under circumstances with decreased ambient temperature.

Westerterp-Plantenga, M.S., Top, S., Cilissen, C. & van Marken Lichtenbelt, W.D. (2001a) Energy metabolism in women during a short exposure to an elevated ambient temperature. *Submitted*.

Westerterp-Plantenga, M.S., van Marken Lichtenbelt W. D., Strobbe, H. & Schrauwen, P. (2001b) Energy metabolism and body weight in humans at a lowered ambient temperature. *Submitted*.

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## RATE SENSITIVITY OF TYMPANIC TEMPERATURE THRESHOLDS FOR VENTILATION DURING EXERCISE-INDUCED BODY WARMING IN HUMAN

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Core temperature thresholds for ventilation during body warming induced by either exercise or hot bath immersion have been demonstrated (White & Cabanac 1996). It was observed at core temperatures greater than these thresholds, that ventilation increased in direct proportion to core temperatures. This supported the hypothesis ventilation behaves as a thermoregulatory response at elevated body core temperatures by giving a response that is proportionate to the increase in core temperature. Based on the rate sensitive responses of temperature sensitive neurons, it has also been suggested that human thermoregulatory responses may be sensitive to the rate of core temperature increase. To test the hypothesis if core temperature thresholds for minute ventilation are sensitive to the rate of core temperature increase, core temperature thresholds for ventilation were determined across at differing rates of core temperature increase. Data from 4 studies and 23 subjects in normothermic conditions ( $T_{\text{ambient}} = 22$  to  $24^{\circ}\text{C}$ , Relative Humidity 40 to 50%) were included in this analysis. In each study subjects pedalled on a seated cycle ergometer and workloads were increased until the point of exhaustion. The work load was increased by differing steps of 17.5 W, 20W, 40W and 52.5 W each 2 min to induce differing rates of either tympanic ( $T_{\text{ty}}$ ) or esophageal ( $T_{\text{es}}$ ) core temperature increase. Skin temperatures, expressed as the unweighted mean, were measured at 4 surface sites including the forehead, upper limb, thorax, and lower limb.  $T_{\text{ty}}$  and  $T_{\text{es}}$  thresholds for minute ventilation, normalised for carbon dioxide production and oxygen consumption, were determined from scatterplots by two (or three if a discrepancy was evident) separate observers. Results showed that the differing rates of workload increase induced differing rates of increase for  $T_{\text{ty}}$  (range: 2.82 to  $5.10^{\circ}\text{C}/\text{hr}$ ) and for  $T_{\text{es}}$  (range: 3.41 to  $6.30^{\circ}\text{C}/\text{hr}$ ). The mean skin temperatures were either constant or increasing during the exercise sessions. High and significant negative correlations between the rate of  $T_{\text{ty}}$  increase and the  $T_{\text{ty}}$  thresholds for  $V_{\text{E}}/\text{VO}_2$  ( $r=-0.72$ ,  $p < 0.01$ ) and for  $V_{\text{E}}/\text{VCO}_2$  ( $r=-0.92$ ,  $p < 0.01$ ) were evident. Correlations between the rate of  $T_{\text{es}}$  increase and the  $T_{\text{es}}$  thresholds for  $V_{\text{E}}/\text{VO}_2$  and for  $V_{\text{E}}/\text{VCO}_2$  were low and not significant. The results supported that  $T_{\text{ty}}$  thresholds for ventilation are sensitive to the rate of core temperature increase. The same result was not apparent for  $T_{\text{es}}$  thresholds for ventilation. In conclusion, the evidence supports that  $T_{\text{ty}}$  thresholds for ventilation are sensitive to the rate of  $T_{\text{ty}}$  increase. A higher rate of core temperature increase gave a lower core temperature threshold for minute ventilation in these exercise conditions.

White, M.D. & Cabanac, M. (1996) Exercise Hyperpnea and hyperthermia in human. *Journal of Applied Physiology*, 81, 1249-1254.

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## COMPARISON OF CORE TEMPERATURE THRESHOLDS FOR VENTILATION TO VENTILATION THRESHOLDS 1 AND 2 DURING INCREMENTAL EXERCISE IN HUMANS

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Human ventilation during a progressive exercise to maximal attainable levels, expressed as a function of oxygen consumption ( $VO_2$ ), shows two successive inflection points or ventilation thresholds (VT). Employing the terminology of Skinner-McLellan-Kinderman, the lower ventilation threshold ( $VT_1$ ) is suggested to coincide with the onset of blood lactate accumulation and the upper ventilation threshold ( $VT_2$ ) is possibly of a neurogenic origin. At close to 70-80% of the maximal attainable work-rate, core temperature thresholds for ventilation were also demonstrated (White & Cabanac 1996). However, it is not known if the work rates at these core temperature thresholds for ventilation are the same or different than the work rates at  $VT_1$  and  $VT_2$ . The purpose of the present study was to compare the  $VO_2$  at the core temperature thresholds for ventilation to both  $VT_1$  and  $VT_2$ . The goal was to address if these three separate ventilation thresholds are similar or different physiological or metabolic responses. Six fit male, college-aged subjects pedaled a cycle ergometer on 2 occasions in progressive exercise tests until the point of exhaustion. In one exercise session work rate was increased by 20W/2 min (slow ramp) and in the other by 40W/2 min (fast ramp). Subjects were instrumented for esophageal temperature ( $T_{es}$ ), skin temperatures and their expired gases were collected to assess oxygen consumption ( $VO_2$ ), carbon dioxide production ( $VCO_2$ ) and minute ventilation ( $V_E$ ). In both exercise sessions, ventilatory equivalents for oxygen consumption ( $V_E/VO_2$ ) and carbon dioxide production ( $V_E/VCO_2$ ) were plotted as a function of both  $T_{es}$  and  $VO_2$ . These plots allowed the determination of  $VO_2$  at each of the  $T_{es}$  threshold for ventilation,  $VT_1$  and  $VT_2$ . In the slow ramp session the  $VO_2$  of  $2.85 \pm 0.23$  l/min at the  $T_{es}$  threshold for  $V_E/VO_2$  ( $p < 0.01$ ) and the  $VO_2$  of  $2.44 \pm 0.19$  l/min at the  $T_{es}$  threshold for  $V_E/VCO_2$  ( $p < 0.01$ ) were significantly greater than the  $VO_2$  of  $1.81 \pm 0.11$  l/min at  $VT_1$ . In the fast ramp session the  $VO_2$  of  $2.87 \pm 0.16$  l/min at the  $T_{es}$  threshold for  $V_E/VO_2$  ( $p < 0.001$ ) and the  $VO_2$  of  $2.68 \pm 0.15$  l/min at the  $T_{es}$  threshold for  $V_E/VCO_2$  ( $p < 0.01$ ) were both significantly greater than the  $VO_2$  of  $1.15 \pm 0.23$  l/min at  $VT_1$ . Comparisons of  $VO_2$  at the  $T_{es}$  threshold for ventilation to  $VO_2$  at  $VT_2$  gave different results. In the slow ramp session the  $VO_2$  at the  $T_{es}$  threshold for  $V_E/VO_2$  was not significantly different than the  $VO_2$  of  $3.01 \pm 0.17$  l/min at  $VT_2$ . The  $VO_2$  at the  $T_{es}$  threshold for  $V_E/VCO_2$  in the same slow ramp session was significantly lower ( $p < 0.01$ ) than  $VT_2$ . In the fast ramp session the  $VO_2$  at the  $T_{es}$  thresholds for  $V_E/VO_2$  and  $V_E/VCO_2$  were both not significantly different than the  $VO_2$  of  $2.71 \pm 0.18$  l/min at  $VT_2$ . In conclusion, the  $VO_2$  at the  $T_{es}$  thresholds for ventilation is significantly greater than the oxygen consumption at  $VT_1$  and appears not to be different than oxygen consumption at  $VT_2$ . The results appear to support that  $VT_1$  is a ventilatory response occurring at significantly lower  $VO_2$  than either  $VT_2$  or the  $T_{es}$  threshold for ventilation.

White, M. D. & Cabanac, M. (1996) Exercise Hyperpnea and hyperthermia in human. *Journal of Applied Physiology*, 81, 1249-1254.

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## COMPARISON OF CORE TEMPERATURE THRESHOLDS FOR VENTILATION TO A POINT OF INCREASED BLOOD LACTATE ACCUMULATION DURING INCREMENTAL EXERCISE IN HUMANS

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During progressive exercise blood lactate levels begin to increase as the intensity of exercise increases. At higher levels of incremental exercise one view supports that increase in ventilation, relative to metabolic need, is a respiratory compensation for the lactic acidosis. Employing the terminology of Skinner-McLellan-Kinderman this respiratory compensation is initiated at the first ventilation threshold ( $VT_1$ ) at approximately 30-50% of maximal oxygen consumption. Core temperature thresholds for ventilation during incremental exercise have also been identified (White & Cabanac 1996) and core temperature is suggested to be an additional stimulus to ventilation at levels of exercise greater than about 70% of maximal oxygen consumption. It is not yet known how these core temperature thresholds for ventilation compare to the point of elevated blood lactates during incremental exercise. The purpose of this study was to compare the level of oxygen consumption ( $VO_2$ ) at the core temperature threshold for ventilation to that at the point of blood lactate accumulation during incremental exercise. Six fit male college-aged subjects pedaled a cycle ergometer on 2 occasions in incremental exercise tests until the point of exhaustion. In one session the power output was increased by 20W/2 min (slow ramp) and in the other by 40W/2 min (fast ramp). Subjects were instrumented for esophageal temperature ( $T_{es}$ ), skin temperatures and their expired gases were collected to assess  $VO_2$ , carbon dioxide production ( $VCO_2$ ) and minute ventilation ( $V_E$ ). At each workload two arterialized blood samples were taken from the tip of the finger and subsequently analysed for blood lactate concentrations. In both exercise sessions, ventilatory equivalents for oxygen consumption ( $V_E/VO_2$ ) and carbon dioxide production ( $V_E/VCO_2$ ) were plotted as a function of both  $T_{es}$  and  $VO_2$ . From 2 independent observations of these plots (or by 3 if a discrepancy was evident) the  $VO_2$  at the  $T_{es}$  threshold for ventilation in each exercise session was assessed. In addition, visual inspection of scatterplots of blood lactate levels versus  $VO_2$  allowed determination of the  $VO_2$  at the 2-mmol blood lactate point. In the slow ramp session the  $VO_2$  of  $1.51 \pm 0.14$  l/min at the 2-mmol point was significantly less than both the  $VO_2$  of  $2.85 \pm 0.21$  l/min ( $p < 0.001$ ) at the  $T_{es}$  threshold for  $V_E/VO_2$  and the  $VO_2$  of  $2.44 \pm 0.19$  l/min at the  $T_{es}$  threshold  $V_E/VCO_2$  ( $p < 0.001$ ). This was also evident in the fast ramp session when the  $VO_2$  of  $0.86 \pm 0.12$  l/min at the 2mmol point of lactate accumulation was significantly less than the  $VO_2$  at the  $T_{es}$  thresholds for  $V_E/VO_2$  ( $p < 0.001$ ) and for  $V_E/VCO_2$  ( $p < 0.001$ ). In conclusion, the  $VO_2$  at the 2-mmol point of blood lactate accumulation is significantly less than the  $VO_2$  observed at the esophageal temperature threshold for ventilation during incremental exercise to maximal attainable work-rates. The results support that the accumulation of blood lactate and the  $T_{es}$  thresholds for ventilation are separate events with potentially different metabolic and/or neural origins.

White, M.D. & Cabanac, M., (1996) Exercise hyperpnea and hyperthermia in human. *Journal of Applied Physiology*, 81, 1249-1254.

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## THE EFFECT OF FACE FANNING ON CONTINUOUSLY MEASURED BRAIN AND EXTRACRANIAL TEMPERATURES IN HUMANS

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The estimate of intracranial temperatures from extracranial core temperature measurement sites remains an enigma. In clinical settings the estimate of intracranial temperatures in feverish, post-operative patients is critical since the prognosis for these hyperthermic patients is often very poor. The best indicator of intracranial temperatures from an extracranial core temperature site is needed to allow appropriate monitoring and care of these patients. Very few direct intracranial measurements of humans have been reported in the literature. As such the purpose of the present investigation was to assess the degree of association between intracranial temperatures and both tympanic and esophageal temperatures. In addition, the effects of face fanning on these continuously measured intracranial and extracranial temperatures were assessed. The subjects included 14 post-operative patients following surgery and all patients had intact and closed craniums. The patient group included feverish, non-feverish and normothermic patients. The patients' were followed in three conditions. First their temperatures were recorded prior to face fanning. Next, their faces were fanned for 20 to 30 min with a small fan at an air speed of  $3.25 \text{ m}\cdot\text{s}^{-1}$ . Subsequently the patients' temperatures were followed after the fanning period. The results demonstrated that intracranial temperature changes measured in the subdural space (Tsd) and epidural space (Ted) were highly correlated ( $r=0.93$ ,  $p < 0.05$ ) to changes in tympanic temperatures (Tty) and uncorrelated to changes in esophageal temperatures. The drop in tympanic temperature of  $0.18 \pm 0.03^\circ\text{C}$  was also not significantly different than the mean drop of intracranial temperature of  $0.15 \pm 0.05^\circ\text{C}$  during the face fanning period. In this study the face fanning of patients with intact craniums demonstrated changes of intracranial temperatures that followed tympanic temperatures more closely than esophageal temperatures.

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## CYCLIC GMP EFFECTS ON NEURONAL THERMOSENSITIVITY AND FIRING RATE IN RAT HYPOTHALAMIC TISSUE SLICES

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The rostral hypothalamus contains temperature sensitive and insensitive neurons, and this region plays an important role in thermoregulation and fever. It is possible that endogenous signals modify the activity of these neurons by intracellular cyclic nucleotides. Previous *in vitro* studies in our laboratory found that cyclic AMP increased the firing rate and thermosensitivity of hypothalamic warm sensitive neurons; however, cAMP had little effect on temperature insensitive neurons. The present study tested the responses of hypothalamic neurons to a different cyclic nucleotide, cGMP. Extracellular action potentials were recorded in hypothalamic tissue slices prepared from male, Sprague-Dawley rats. Each rat was killed by decapitation, the brain was removed, and a block containing the hypothalamus was cut. Horizontal tissue slices (350 microns thick) were sectioned and transferred to a recording chamber perfused with an oxygenated (95% O<sub>2</sub>-5% CO<sub>2</sub>), 300 mOsm/kg nutrient medium. The experimental medium was similar to the control medium but contained 8-bromo-cGMP (5-100  $\mu$ M), a membrane permeable cyclic GMP analog. The perfusion medium and tissue slices were maintained at 36°-37°C using a thermoelectric assembly that also allowed periodic warming and cooling to characterize neuronal thermosensitivity. Single unit activity was recorded at various hypothalamic locations, including the preoptic area and anterior hypothalamus. Each neuron was characterized according to its thermosensitivity; i.e., its change in firing rate (Hz or imp/sec) during a change in tissue temperature. Neurons with a thermosensitivity of at least 0.8 imp/sec/°C were considered to be warm sensitive. Neurons having lesser thermosensitivities were grouped into subpopulations of temperature insensitive neurons; i.e., low-slope temperature insensitive neurons were less than 0.2 imp/sec/°C, while moderate-slope temperature insensitive neurons were at least 0.2 imp/sec/°C but less than 0.8 imp/sec/°C. Each neuron's spontaneous firing rate and thermosensitivity were tested before, during and after 8-bromo-cGMP perfusion. Low concentrations of 8-bromo-cGMP did not affect the firing rates of most warm sensitive neurons but either increased or decreased the firing rates of many temperature insensitive neurons. On the other hand, 8-bromo-cGMP did not affect the thermosensitivity of low-slope temperature insensitive neurons but either increased or decreased the thermosensitivity of many warm sensitive and moderate-slope temperature insensitive neurons. In addition to neuronal thermosensitivity, cGMP also affected neuronal responses to CO<sub>2</sub>. Some neurons changed their firing rates when CO<sub>2</sub> concentration was increased to 10% (from a control concentration of 5% CO<sub>2</sub>), and 8-bromo-cGMP altered this response to CO<sub>2</sub>. In general, it appears that both cGMP and cAMP modify thermosensitivity in those neurons that are highly sensitive or moderately sensitive to temperature. In terms of firing rates, however, cGMP has its predominant effect on the least thermosensitive neurons, while cAMP primarily affects the most thermosensitive neurons.

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## STUDY ON THE POSSIBILITY OF ANTIBODIES AGAINST HEAT STRESS PROTEINS AS BIOMARKERS TO ASSESS ABNORMAL XENOBIOTIC-INDUCED STRESS

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Heat shock or stress proteins (Hsps) are a group of proteins induced by a large of xenobiotics, many of which are common in the working environment. The important biological functions of Hsps are closely related to thermatolerance or poison tolerance. The present aim in this paper is to explore the possibility of antibodies against as biomarkers to assess whether workers are experiencing or have experienced abnormal xenobiotics-induced stress within their working environment. In the present study, We used immunoblotting to investigate the presence of antibodies against the different Hsps, Hsp27, Hsp60, Hsp71, Hsc (heat shock cognate) 73, Hsp90 $\alpha$  and  $\beta$  in groups of workers exposed to high temperature, carbon monoxide, to either low ( $<300$  mg/m<sup>3</sup>) or high concentrations of benzene (300 mg/m<sup>3</sup>) and a group of workers who had experienced benzene poisoning. In the same time, blood samples from this workers were assayed for the number of peripheral white blood cells, concentration of hemoglobin, activities of serum superoxide dismutase (SOD), lymphocyte DNA damage et al. We further investigated the difference in oral temperature, heart rate, and lymphocyte DNA damage in the man-made climate high temperature room between pilot with and without anti-Hsps. The significance of the presence and dilution of anti-Hsp71 were analyzed in patients with heat inducing illness using western blot-ELISA. Antibodies to Hsp27 and Hsp71 were found more frequently in the high temperature and carbon monoxide-exposed groups than in control ( $P<0.05$ ). The carbon monoxide-exposed group showed the highest incidence of anti-Hsp antibodies. Anti-Hsp60 antibodies were only detected in workers exposed to high temperature and carbon monoxide. The high incidence of anti-Hsp was related to the percentage of workers with abnormal electrocardiogram, B echogram changes, displaying hepatitis B antigen, a significant increase in the activities of ananine aminotransferase and acid phosphatase, and a significant increase in lymphocyte DNA damage. Benzene-poisoned workers showed a high incidence of antibodies against Hsp71 (~40%) which was associated with a decrease in white blood cells ( $3.84 \pm 1.13 \times 10^9$  versus  $7.68 \pm 1.84 \times 10^9$  in control) and with an increase in activities of serum SOD ( $138.43 \pm 23.15 \text{ U/ml}$ ) and lymphocyte DNA damage (18.7%). The results from the man-made climate room showed that the increase in oral temperature, heart rate and lymphocyte DNA damage in pilots with the positive antibodies to Hsp were higher than those in pilots with the negative antibodies during heat stress. The presence and dilution of anti-Hsp71 in patients with acute heat inducing illness were significantly higher than in control. These results suggest that the increased frequency of antibodies to Hsps is the result of these damage, of the release of denatured Hsps and of a decrease in the phagocytic ability of macrophages in these worker and the presence of these autoantibodies in plasma of workers and pilots may indicate the increase of heat damage and high sensitivity to heat or others. These results also suggest that whether antibodies against Hsps can potentially be useful biomarkers to assess if workers are experiencing abnormal stress within their living and working environment.

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## **PRESENCE OF ANTIBODY AGAINST THE INDUCIBLE HEAT SHOCK PROTEIN HSP71 IN PATIENTS WITH ACUTE HEAT INDUCED ILLNESS**

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Antibodies against heat shock or stress proteins (Hsps) have been reported in patients with a number of diseases where they may be involved in the pathogenesis of disease or may be of use for prognosis. Heat-induced diseases such as heat cramps, heat exhaustion or heat stroke are frequent in hot working or living environments. There are still few investigations on the presence and possible significance of autoantibodies against heat shock proteins in heat-induced illnesses. Using an immunoblotting technique with recombinant human Hsps, we have looked for the presence and measured titers of antibodies against Hsp60, Hsp71, and Hsp90 $\alpha$  and  $\beta$  in 42 young patients with acute heat-induced illness. We also examined the presence of antibody against Hsp71 in 57 older patients with acute heat-induced illness and the changes in titers of anti-Hsp71 antibodies in 9 patients hospitalized by emergency physicians. In the group of young persons exercising in a hot environment, the occurrence of antibodies against Hsp71 and Hsp90 $\alpha$  was significantly higher among individuals with symptoms of heat-induced illness ( $P<0.05$ ) than in the matched group of non-affected exercising individuals. Moreover the titers of antibody against Hsp71 were higher in individuals of the severe and mild heat-induced illness groups, the highest titer being found in the most severe cases. A study of a second group of 57 older heat-affected patients exposed to extreme heat gave similar results. Again patients with the more severe heat-induced symptoms showed a significantly higher incidence of antibodies to Hsp71 than controls and the titer of anti-Hsp71 was higher in the severely affected group. Finally in a study of 9 patients, it was observed that the titer of anti-hsp71 decreased during recovery from severe heat symptoms. These results suggest that measurement of antibodies to Hsps may be useful to assess how individuals are responding to abnormal stress within their living and working environment and may be used as one of biomarkers to evaluate the susceptibility to heat-induced diseases.

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## **BASAL AND INDUCIBLE LEVEL OF HSP71 IN PERIPHERAL BLOOD LYMPHOCYTES IN SOLDIER WITH HEAT INDUCED ILLNESS**

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The objective of this research was to analyse the basal and inducible level of HSP71 in peripheral blood lymphocytes in heat-induced illness and control soldiers, and to explore the mechanism of heat induced illness. Flow Cytometry was used for detecting HSP71 in peripheral blood lymphocytes. In the basal condition, the level of HSP71 was low, and no significance was found between the control and heat-induced illness soldiers (268.10, 390.05). After being cultured at 37°C for 5h, the level of HSP71 in both the heat illness and control soldiers remarkably increased compared with the basal condition. The level of HSP71 of heat-induced illness soldiers was much higher than control (1405.08 and 931.16,  $P<0.01$ ). HSP71 in control soldiers increased slightly after stressed at 41°C for 1h (955.99), while in heat-induced illness group, HSP71 declined instead of reaching a high level (1148.92). It may be concluded that the inducibility of HSP71 changed in the cases with heat-induced illness. This suggests that the individual differences of the HSP71 gene and expression may play a role in the occurrence of heat-induced illness. The threshold of thermotolerance decreased and the ability of thermotolerance could not normally formed.

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## HUMAN BRAIN TEMPERATURE REGULATION AND OXIDATIVE METABOLISM DURING FUNCTIONAL VISUAL STIMULATION

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A fundamental discovery of modern human brain imaging with positron emission tomography (PET) that the blood flow to activated regions of the normal human brain increases substantially more than the oxygen consumption (Fox et al., 1986) has lead to a broad discussion in the literature concerning possible mechanisms responsible for this phenomenon. Presently no consensus exists. It is well known that oxygen delivery is not the only function of systemic circulation. Additional roles include delivery of nutrients and other required substances to the tissue, waste removal, and temperature regulation. Among these other functions, the role of regional cerebral blood flow (rCBF) in local brain temperature regulation has received scant attention. Here a theoretical analysis is presented supported by empirical data obtained from humans with functional magnetic resonance (fMR) suggesting that increase in rCBF during functional stimulation can cause local changes in brain temperature and subsequent changes in oxygen consumption. Major factors contributing to temperature regulation during functional stimulation are changes in the oxygen consumption, changes in the temperature of incoming arterial blood and heat exchange between activated and surrounding tissue. The water proton magnetic resonance (MR) frequency temperature-shift of  $-0.01 \text{ ppm}/^{\circ}\text{C}$  was employed to monitor local brain temperature changes in human volunteers during functional activation. The MR data were collected on a 1.5 tesla Siemens Magnetom Vision scanner using a single voxel localization technique that allows estimation of both water signal intensity and signal frequency (Yablonskiy et al., 2000). A typical voxel size was 10 ml and experimental repetition period was 2 sec. The functional activation paradigm included 4 min of rest, followed by 4 min of visual cortex stimulation using GRASS goggles flashing at 8 Hz, followed by a final 4 min. of rest. MR signal intensity and signal frequency (temperature) both change during functional activation. Local brain temperature decreases on average by about  $0.2^{\circ}\text{C}$  during activation, however, individual variations up to  $\pm 1^{\circ}\text{C}$  have also been observed. An important feature of all data is a strong correlation ( $R=0.94$ ) between the slope that characterizes the change in signal intensity with time and the slope that characterizes the change of signal frequency with time during the activation period. This effect offers additional evidence of brain temperature changes during functional activation. Indeed, change in brain temperature results in change in the rate of chemical reactions, hence tissue metabolism, hence venous blood oxygen saturation, hence MR signal intensity. A MR microcirculation model (Yablonskiy et al., 1994), allows estimation from this data of a mean change in metabolic reaction rate on the order of 8% per  $1^{\circ}\text{C}$ , which is in agreement with published data (Swan, 1974).

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## **THERMAL CONDITIONING AT THE POSTNATAL STAGE – A POSSIBLE TREATMENT TO INCREASE THERMOTOLERANCE IN FAST GROWING CHICKENS**

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Following a tremendous genetic improvement during the last decades, broiler chickens improved significantly their growth rate in a relatively short period. It coincided with higher metabolic rate and increased sensitivity to sub-optimal conditions, such as high ambient temperature ( $T_a$ ) or extreme relative humidities (rh). Acclimation to elevated  $T_a$  impairs broilers' performance and partially diminishes the genetic improvement. However, short-term exposure to mild heat stress (thermal conditioning - TC) during the first week post hatch was found to improve both the acquisition of thermotolerance and performance. The technique of TC takes advantage of the immaturity of the mechanism to regulate body temperature ( $T_b$ ) in young chicks during their first week of life. Thermal conditioning to mild heat stress during the first week of life ( $T_a=37.5\pm1.0^\circ\text{C}$ ; 70-80% rh; for 24 h at the age of 3 days) resulted in growth retardation followed by an immediate compensatory growth, which resulted in complete compensation for the loss of weight gain, leading to higher body weight and breast muscle of the conditioned chickens at the age of 42 days. TC causes an increase in skeletal muscle satellite cell activity, necessary for further muscle hypertrophy. An immediate increase was observed in satellite cell DNA synthesis in culture and in breast muscle tissue (removed from dead chicks) in response to TC, to levels that were significantly higher than that of non-treated chicks. This was accompanied with the induction of insulin-like growth factor-I (IGF-I), but not hepatocyte growth factor (HGF) in the TC chicks, followed by a significant elevation of number of cells per gram of muscle. To study the effect of TC on thermotolerance acquisition, chickens at the age of 42 days (the approximate market age) were thermally challenged (6 h exposure to  $T_a=35\pm1.0^\circ\text{C}$  and 20-30% rh). Thermal challenge resulted in hyperthermia and mortality. However, while in the control chickens hyperthermia reached  $T_b$  of  $45.3\pm0.08^\circ\text{C}$ , in TC chickens  $T_b$  increased to only  $44.3\pm0.23^\circ\text{C}$  with significantly lower mortality. TC chickens demonstrated lower plasma triiodothyronine and thyroxine concentration suggesting a reduction in heat production. It coincided with significantly higher heat loss by radiation and convection. During thermal challenge the stress effect in the TC chickens was significantly lower as suggested from plasma concentration of corticosterone, glucagon and IGF-II. A significantly lower induction of heat shock proteins (70 and 90 kDa) synthesis in heart muscle and lung tissues (removed from dead birds) of TC chickens further suggests that these birds suffer less from heat stress. It can be concluded that thermal conditioning at the age of 3 days post hatch improves dramatically the ability of the mature chickens to thermoregulate during exposure to acute heat spells and even improves chick performance.

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## THERMOREGULATORY RESPONSES OF CHILDREN AND YOUNG ADULTS IN A HOT ENVIRONMENT

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Because of their greater body surface area (BSA)-to-Body mass (BM) ratio, children have physical advantage for heat loss than adults. Some researchers reported that children tend to depend on dry heat loss rather than evaporating cooling under hot thermal conditions. There are, however, few detailed descriptions of the mechanisms of children's thermal responses. Our study includes 29 children (16 boys and 15 girls: 7-10 of age; children group) and 16 students (8 males and 8 females: 20-24 of age; adults group). A consent form was signed by each students and children's parents. They were placed in a pre-room set at 28°C, 50%RH, after that, they were moved to an exposure room set at 30°C, 70%RH, where they immersed their legs in a 42°C-water-bath during the last 40 minutes. Measured during the experiments were rectal temperature (Tre), skin temperature at 7 sites, local sweat rate on the back (Lsw,b) and forearm (Lsw,f), forearm skin blood flow (FSBF) and body weight loss (as total sweat rate). Mean skin temperature (Tsk) was calculated the following equation:  $Tsk = (7*Tforehead + 18*Tchest + 17*Tback + 15*Tforearm + 5*Thand + 25*Tthigh + 13*Tfoot)/100$ . At the onset of sweating, forearm skin temperature (Tforearm) decreased slightly for the adults groups. In contrast, it increased for the children group. The FSBF of the children group increased significantly greater than in the adults group during the immersion. Hence the linear regression line between FSBF and Tforearm was up for the children group, and down for the adults group. A similar tendency was observed the relationship between Lsw,f and Tforearm. On the other hand, there were no such differences on the back between the children group and adults group. During the immersion, Tsk of the children group was kept at higher level than the adults group, while that of the adults group was gradually decreased. As for Tsw/BSA and Tsw/BM, there were no significant differences between the groups. Still, the adults group had greater increase in Tre than the children group. These results suggest that the children have an advantage in preventing the rise of Tre, despite the fact that the adults had more efficient evaporative cooling. Because there were no differences in Tsw/BSA and Tsw/BM among the groups, it was supposed that the children's efficiency of sweating was approximately equal to the young adults. Therefore, the relationship between FSBF and Tforearm, Lsw,f and Tforearm may indicates that the children's higher skin temperature was caused by greater forearm skin blood flow rather than by less Lsw,f and/or Lsw,b. Since the children kept their Tsk at a higher level, dry heat loss may work effectively for them under the thermal conditions of the exposure room (30°C, 70%RH). In conclusion, the children may have advantage to inhibit rising their Tre compared to young adults under a hot thermal conditions, which dry heat loss works effectively than evaporative cooling, for their greater responses on skin blood flow.

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## VASOMOTOR RESPONSES DURING SINUSOIDAL EXERCISE IN GLABROUS AND NONGLABROUS HUMAN SKIN

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Reflex control of the vasculature in nonglabrous skin is mediated by a vasoconstrictor system and an active vasodilator system, whereas that in glabrous skin is mediated by a vasoconstrictor system only. In the present study, to test whether vasomotor responses to dynamic exercise differ in glabrous and nonglabrous human skin, we determined the phase response and amplitude response of cutaneous vascular conductance (CVC) in dorsal hand, forearm and palm to sinusoidal exercise. Nine healthy subjects exercised on a cycle ergometer with a constant load (35 % of peak O<sub>2</sub> uptake) for 20 min; for the next 40 min they exercised with a sinusoidal load at an ambient temperature of 25 C and relative humidity of 60 %. The sinusoidal load variation ranged from 10 % to 60 % of peak O<sub>2</sub> uptake over a 4-min period. Skin blood flow was monitored by laser-Doppler flowmetry. CVC was evaluated from the ratio of blood flow to mean arterial pressure. During sitting rest and exercise, CVC in dorsal hand and forearm showed lower values than that in palm (P<0.05). During sinusoidal exercise, the amplitude in CVC in palm was three times and forty six times greater than those in dorsal hand and forearm, respectively (P<0.05). The phase lags in CVC in dorsal hand (58±14 s) and forearm (76±17 s) were smaller than that in palm (135±6 s) (P<0.05), because CVC in palm was decreased promptly with the increase of exercise load. These findings suggest that nonglabrous skin vasomotor shows a smaller amplitude response and prompter phase response than glabrous skin vasomotor during cyclic changes of dynamic exercise load. The difference of cutaneous vasomotor control in glabrous and nonglabrous regions during dynamic exercise may be partly due to active vasodilator system.

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## **EFFECTS OF OREXIN-A ON RAT THERMOREGULATION: THE ROLES OF PROSTAGLANDIN E<sub>2</sub>**

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The hypothalamus plays a central role in the integrated control of thermoregulation. A novel neuropeptides called orexins have been identified and distributed densely in the hypothalamus. The present study wants to elucidate the mechanism of orexin on thermoregulation. Male Sprague-Dawley rats were used in this study. The effects of orexin on colonic temperature in unanesthetized rats acclimated to a rat restraining stock. Colonic temperature was measured by using copper-constantan thermocouples. Cerebral prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) was determined by ELISA. All drugs were prepared in pyrogen-free glassware and containers. Intracerebroventricle administration of orexin induced dose-dependent rise in the colonic temperature. Pretreatment of indomethacin, a PGE<sub>2</sub> synthesis inhibitor, significantly attenuated the fever induced by orexin injection. Our results suggest that the effect of orexin on thermoregulation were mediated by PGE<sub>2</sub>.

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## THE EFFECT OF AMBIENT TEMPERATURE ON THERMOREGULATION AND PERFORMANCE DURING PROLONGED INTERMITTENT EXERCISE

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Environmental heat is known to increase the body temperature and reduce aerobic performance (Galloway & Maughan, 1997; Parkin et al., 1999). However, it is not clear whether performance of prolonged intermittent exercise is affected by a hot environment. The aim of this study was to investigate the effect of ambient temperature on thermoregulation and performance during prolonged intermittent exercise.

Seven trained men underwent three identical intermittent exercise protocols in cool (15°C), neutral (25°C) and hot (35°C) conditions, in a constant 60 % humidity condition. The cycle ergometer exercise consisted of a series of eighty 5 sec maximum sprints separated by 25 sec active recovery and 30 sec passive recovery between sprints. Subjects rested for 15 min between the forty and forty-first set. The subjects ingested the same total volume of water before warm up (200 ml), before exercise (300 ml) and half time (500 ml). We evaluated performance by peak power output and mean power output during sprints. To examine the thermoregulation function during exercise, quantitative analysis was made for heat production, heat losses through convection, conduction and evaporation, and heat storage during exercise.

Peak power output and mean power output in a hot condition ( $11.88 \pm 1.06$  and  $10.35 \pm 0.72$  W/kg) was significantly lower than in a cool ( $12.56 \pm 0.95$  and  $10.91 \pm 0.68$  W/kg) or neutral condition ( $12.50 \pm 1.05$  and  $10.74 \pm 0.74$  W/kg). Evaporative heat loss was increased and non-evaporative heat loss was decreased with increase in environment temperature. However, heat storage in hot condition was higher than in neutral condition. The increase in rectal temperature in a hot condition was significantly higher than in a cool or neutral condition. It was apparent that the higher the increase in body temperature, the lower the power output during sprints. No significant differences were observed between the three conditions for rating of perceived exertion and thirst ratings (Thompson et al., 1986). These results suggest that performance of prolonged intermittent exercise is affected by a hot environment.

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## REGULATORY EFFECT OF SKIN BLOOD FLOW RESPONSE TO MILD COLD

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The basis of regulatory effect of skin blood flow is the decrease of circulating blood in the surface of human body. In severe cold environment it is occurred simultaneously with shivering that is why it is difficult to separate the role of skin blood flow response. In mild cold environment vascular skin response is the only way to cope disturbance. The aim of this study is to evaluate thermoregulatory efficiency of skin blood flow response to mild cold exposure. It is developed mathematical model of human thermoregulation, which comprises active and passive processes of heat production, heat transfer via blood and conduction between organs, heat-exchange with environment. Skin blood flow is performed by additive proportional control following brain and skin temperatures changes. Mathematical model is the system of usual differential equations which allows to calculate organs and tissues temperatures in transient and steady-state. Modeling researches were performed in air temperature varying from neutral 29°C to 15°C for clothing 0.3 clo. To evaluate effect of skin blood flow response of organism in mild cold it was considered the coefficient of regulatory efficiency  $K_e$ . It is the ratio of temperature deviation in any organ from initial value in theoretical case of absence of skin vasoconstriction to temperature deviation from initial value in presence of this response.

$$K_e = \left| \frac{T_i^* - T_i}{T_i^* - T_i^R} \right|$$

where  $T_i^*$  – initial organ temperature in neutral environment,  $T_i$  – temperature of this organ at cold exposure without skin blood decrease (i.e. without regulatory response),  $T_i^R$  – organ temperature for skin blood flow decrease (presence of regulatory response). Coefficients  $K_e$  were calculated for all organs and parts of the body at different mild cold exposures and were the subject of the analysis. Results of modeling as follows. The coefficient  $K_e$  differs greatly for core and shell of body.  $K_e$  shows regulatory influence of skin blood flow changes on the parameters of temperature homeostasis. For brain, blood and internal organs temperatures  $K_e$  increased as far as skin blood flow decreases (20%, 30%) and got maximum at 40% decrease from initial value.  $K_e$  increased in 2 times for brain temperature and in 4 times for blood and internal organs temperatures. Modeling results shows that vascular skin response to mild cold exposure is considerably effective for core temperatures. These temperatures are sensitive to skin blood flow and as a result insignificant decrease of skin blood flow allows to maintain core temperatures close to initial values. Influence of skin blood flow response on skin temperatures is less than to core temperature. Results of modeling show that ambient temperature prevails in influence on skin temperatures. For 40% decrease of skin blood flow (from 9 l/h to 5,7 l/h)  $K_e$  practically does not differ. It may concludes. This modeling result has important physiological importance: the main significance of skin blood flow response to mild cold is the decrease of heat transfer by blood but not heat conduction in skin.

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## NEURONS IN THE PREOPTIC AREA EXPRESSING C-FOS DURING COLD/WARM EXPOSURE AND PROJECTING TO THE PERIAQUEDUCTAL GREY

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The Preoptic area (PO) plays a key role in body temperature regulation by integrating information about local brain and other body temperatures, and by sending efferent signals to various effector organs. This area contains thermosensitive neurons, which change their activities with change in local brain temperature. In rats thermoregulatory skin vasodilation is elicited mainly by the activation of warm-sensitive neurons, since glutamate injection into the PO elicits vasodilation and procaine injected there elicits vasoconstriction. On the other hand shivering and non-shivering thermogenesis seem to be controlled by the inhibitory signals of warm-sensitive neurons (Kanosue et al., 2000). Skin vasodilative neurons are located in the midbrain periaqueductal grey (PAG), especially in its rostral part (rPAG) (Zhang et al., 1997). And recently we found that the caudal PAG (cPAG) contains neurons generating excitatory signals for non-shivering thermogenesis. However, the direct connections between the PO and the PAG in terms of thermoregulation has not been well documented. In the present study, we investigated the distribution of neurons in the PO activated by cold/warm exposure and projecting to the rPAG or cPAG. Male crj- Wistar rats (300-350 g; Charles River Japan, Osaka Japan) were used. Under the anesthetia with sodium pentobarbital (50 mg/kg, *i.p.*), retrograde tracer, cholera toxin- b (CTb) was injected into the rPAG (0.4 mm from midline, 5.2 mm to bregma and 6.4 mm below the skullface) or the cPAG (0.8 mm, 8.4 mm, 6 mm). After one week recovery period, rats were exposed to warm ( $T_a = 33^{\circ}\text{C}$ ) or cold ambient temperature ( $T_a = 10^{\circ}\text{C}$ ) for 2.5 hr and then perfused under deep anesthesia for the immunohistochemical analysis of c-Fos protein and CTb. When CTb injection was centered in the rPAG, many cells double-labeled with Fos and CTb were observed in the median preoptic nucleus (MnPO) and the lateral part of the medial preoptic area (MPOL) in the warm-exposed rats but not in the cold-exposed rats. On the other hand, when the tracer injection was centered in the cPAG, double-labeled cells were seen in the lateral preoptic area (LPO) in the cold-exposed rats but not in the warm-exposed rats. These results suggest that different groups of PO neuron are activated by warm- or cold-exposure and project to the rPAG or the cPAG, respectively. These projections would form a part of the efferent pathway for the control of heat loss or heat production.

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## COLD-INDUCED DECREASES IN HUMAN, CIRCULATING LEPTIN, AND IN THE SUBCUTANEOUS ADIPOSE LEPTIN SECRETION RATE

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Leptin is secreted primarily by adipocytes, and is associated with regulating energy expenditure and appetite. Studies have shown cold-induced decreases in both circulating leptin and *ob* gene expression, and an apparent protective effect on body temperature of exogenous leptin during acute cold stress. In this study, we investigated the effects of acute cold-water immersion (*in vivo*) on human plasma leptin concentration, and the effects of incubation temperature (*in vitro*) on leptin secretion from human, subcutaneous adipose tissue fragments. Twelve males underwent daily, 60-90-min chest-deep immersions in 18°C water, for 15 days. Blood samples were collected to determine plasma leptin concentration, while regional body temperatures were continuously recorded. In the *in vitro* study, adipose tissue fragments were incubated at three temperatures (27°, 32° and 37°C), with leptin secretion into the culture medium being determined. Acute cold immersion significantly decreased plasma leptin concentration (-14% at 25 min, -22% at 60 min, both  $P<0.05$ ). A significant positive relationship was found between plasma leptin concentration and the decrease in rectal temperature during immersion ( $P<0.05$ ). Incubation temperature significantly affected leptin secretion rate ( $P<0.05$ ). Leptin secretion (*in vitro*) increased 3.7-fold over the temperature range 27-37°C. A simple modelling approach predicted that, during cold-water immersion, plasma leptin concentration would decrease by 45%, due to the local effects of reduced subcutaneous adipose tissue temperature alone. We suggest that low subcutaneous fat temperatures directly reduce leptin secretion in cold-exposed humans. Given the role of leptin in the regulation of both energy intake and energy expenditure, this would make insulating, colder adipose tissue less 'visible' to central mechanisms regulating energy balance, and hence body composition.

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